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Clinical THYROIDOLOGY

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Clinical Thyroidology

EDITORIAL: REFLECTING ON THE PAST YEAR

The new editors of *Clinical Thyroidology* have now completed our first year. So it is a good time to reflect on what we have written. We have summarized with our analysis and commentary 102 articles published in the past year or in ePub online. The articles we have written cover the broad field of thyroidology, which includes thyroid cancer, hyperthyroidism and hypothyroidism (including the subclinical variants), thyroid dysfunction in pregnancy, orbitopathy, goiter, thyroid nodular disease, cytopathology, imaging, and metabolism. We strived to pick papers that are on the cutting edge of clinical thyroidology and are relevant to clinical practice. We avoided summarizing new translational research unless it was ready for incorporation into clinical practice. Nearly half of the articles have been in the area of thyroid cancer, reflecting the growing literature on this topic. At the ATA meeting in Indian Wells, California, Dr. Ashok Shaha joked that one new paper on thyroid cancer is published every 8 hours, but this may not be an exaggeration. There is still controversy about whether the epidemic of thyroid cancer is mainly due to ascertainment using our excellent tools for detecting it or whether there is a real and substantial increase in the incidence of thyroid cancer. I suspect that the increase is attributable to exposure to unrecognized environmental carcinogens, but there are few new papers on this topic.

We have succeeded in posting each issue near the middle of the month. To accomplish this, we have the able assistance of Debbie Stone, our copy reader and literary stylist, Karen Durland, who puts the articles together into the issue, and Jane Arrington, our web manager. We hope that we have succeeded in making it easy for readers to access the articles whose titles pique their interest. Please note that *Clinical Thyroidology* is easy to search. When you open up the ATA website (www.thyroid.org), ***Clinical Thyroidology* ONLINE** appears in the lower right corner. When you open this, there is a "SEARCH CLINICAL THYROIDOLOGY" window in which you can type a topic or author to search for the article you want to review. We aim to be user-friendly.

We are very interested in feedback from readers about what we have written. Please e-mail us at clinicalthyroidology@thyroid.org. We also welcome your comments on the various clinical guidelines of the ATA. Bryan Haugen, Chair, ATA Thyroid Nodules and DTC Guidelines Task Force is requesting your opinion about previous guidelines and new issues for a third revision of the guidelines on thyroid nodules and cancer in a short questionnaire attached to this issue of *Clinical Thyroidology.*

I am especially grateful to my Associate Editors, who have been innovative, scholarly, critical, and dedicated in our joint efforts to bring you the best in the current thyroid literature in a format that is easy to read and digest.

— Jerome M. Hershman

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IQ SCORES OF CHILDREN EVALUATED BETWEEN AGES 4 AND 14.5 YEARS BORN TO WOMEN WITH SUBCLINICAL HYPOTHYROIDISM WERE SIMILAR TO THE IQS OF CHILDREN BORN TO EUTHYROID TREATED WOMEN

Behrooz HG, Tohidi M, Mehrabi Y, Behrooz EG, Tehranidoost M, Azizi F. **Subclinical hypothyroidism in pregnancy: intellectual development of offspring.** Thyroid 2011;21:1143-7.

SUMMARY

BACKGROUND

The effects of maternal subclinical hypothyroidism (M-SCH) on the neuropsychological development of the offspring are not clear. Neuropsychological deficits in the offspring have been observed in overt maternal hypothyroidism and in infants born to mothers with isolated hypothyroxinemia during the first trimester of pregnancy. In one study, even when pregnant women with hypothyroidism were insufficiently treated with levothyroxine (L-T_4), the intelligence quotient (IQ) scores of their offspring were not different from those of controls. The authors evaluated the intellectual development of children of mothers who had M-SCH while they were pregnant with these children.

METHODS

A total of 62 children born to women with hypothyroidism were recruited. After excluding those <4 years or >15 years of age, 44 children were enrolled in the study. The mothers of these children were part of a subgroup of 90 women with 106 pregnancies out of 441 women with hypothyroidism who were of reproductive age seen in Tehran Endocrine Clinics between 1991 and 2003 and who were observed during gestation. Mothers were receiving L-T_4 before gestation, and their serum thyrotropin (TSH) was kept at ≤2.5 μIU/ml before conception. There were 10 miscarriages. In 2007, a total of 62 children (65%) born to these mothers were recruited for this study. Eighteen children were excluded because they were <4 years or >15 years of age. The remaining 44 children were divided into two groups, based on the mother's serum TSH values during pregnancy: TSH ≤3 mU/L on at least on two occasions in the first half of pregnancy (control group [n = 19]) and TSH >3 mU/L on at least two occasions in the first half of the pregnancy (n = 25), of whom 19 had SCH, and 6 clinical hypothyroidism. One serum TSH >3 mU/L had been detected in each mother of the case group before the 10th week of gestation. Serum TSH and free thyroxine (T_4) and urinary iodine were measured in each child, and seven cognitive performance and IQ tests were performed.

RESULTS

The 19 children of women with subclinical hypothyroidism were compared to the 19 children of euthyroid mothers. The mean age of children was 7.8 years, with a range of 4.0 to 14.5. Case children were similar to control children with respect to sex, age, parental education, maternal age at time of pregnancy and at the time of being diagnosed with hypothyroidism, percentage of mothers with thyroid peroxidase antibodies, mother's L-T_4 dose during pregnancy, gestational age at delivery, birth weight, and duration of breast-feeding. Maternal TSH (mean ±SD) in the subclinical hypothyroid case group during pregnancy was 11.3±5.3 mU/L (range, 3.9 to 27.0) and 1.4±1.0 (0.1 to 2.8) in the controls (P<0.001). Maternal T4 during pregnancy was 9.0±2.1 μg/dl (7.1 to 12.0) in hypothyroid cases versus 11.7± 2.6 (7.6 to 14.3) in controls (P<0.001). Serum TSH, free T_4, and urinary iodine concentrations were similar in the two groups of children. Total IQ, performance IQ, and verbal IQ were similar—20±14, 117±12, and 121±16, respectively, in the case group and 121±11, 120±7, and 117±15 in the control group. Results of cognitive performance tests were similar in the two groups. No relationships were observed between variables and IQ except for the education level of the mother and neonatal weight.

CONCLUSIONS

IQ level and cognitive performance of children born to women with hypothyroidism who were treated with L-T_4 are similar in those whose mothers have M-SCH during pregnancy and those whose mothers have normal serum TSH concentrations during pregnancy.

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IQ SCORES OF CHILDREN EVALUATED BETWEEN AGES 4 AND 14.5 YEARS BORN TO WOMEN WITH SUBCLINICAL HYPOTHYROIDISM WERE SIMILAR TO THE IQS OF CHILDREN BORN TO EUTHYROID TREATED WOMEN

ANALYSIS AND COMMENTARY

Maternal and obstetrical complications and impaired neurologic development in children of mothers with thyroid deficiency have been reported in the past 15 years, although results in the final outcomes are not consistent when studies are compared (1). There are many constraints when assessing and comparing published studies, among them lack of consistency in patient selection, methods of thyroid-function testing, reference ranges in defining thyroid dysfunction, iodine status in a given population, and interpretation of outcomes based on only one thyroid test value at a given gestational age. Few published studies correlate obstetrical events with outcomes in newborns. Although universal screening is not recommended by endocrine and obstetrical societies (2, 3), targeting screening of women at risk for thyroid dysfunction is encouraged, but up to 70% of women with thyroid dysfunction will be missed if targeting screening is used (4). One of the most serious potential complications reported is reduction in IQ scores in children born to women with mild hypothyroidism, reported initially by Haddow et al. (5). In their retrospective study, 62 women, whose thyroid tests were measured at 14 to 16 weeks of gestation, had serum TSH above the 97th percentile; 14 of these women were on L-T_4 therapy at the time blood was drawn and supposedly continued with the same dose during their pregnancies, and 48 of them did not receive levothyroxine treatment. The IQ score of the 62 children, evaluated between 7 and 9 years of age was not significantly different from the IQ score of 124 control children. However, a 7-point decrease in IQ scores was detected in the 48 children whose mothers with hypothyroidism did not benefit from thyroid therapy; 19% of them had IQ scores of less than 85%. This suggests that untreated mothers with perhaps more severe thyroid hypofunction were at higher risk to have children with neuropsychological impairment than were mothers who were receiving therapy, albeit still insufficient to normalize their serum TSH. In the present study by the Azizi group, the authors carefully selected women with hypothyroidism who were receiving thyroid therapy before conception, with the aim to keep their serum TSH ≤2.5 mIU/L before conception, as recommended by recent guidelines (2, 3). However, at time that pregnancy was confirmed, 25 of 44 women with hypothyroidism (56.8%) who were taking L-T_4 at conception had a serum TSH >3.0 μIU/ml , which supports the finding of the study by Abalovich et al. (6) that a serum TSH ≤1.3 μIU/ml before conception is necessary in the majority of women with hypothyroidism who are on L-T_4 therapy in order to achieve a serum TSH ≤2.5 mIU/L at the time of the first obstetrical visit. The total IQs of the children of the 19 women with subclinical hypothyroidism, as well as the performance and verbal IQ scores, were not significantly different from those of the control group, which consisted of children of mothers with a serum TSH <3 mIU/L at the first obstetrical visit. No information is given about the 6 children whose mothers had clinical hypothyroidism. A report from the Controlled Antenatal Thyroid Screening (CATS) (7) study was presented at the most recent ATA meeting by John Lazarus; it suggested no difference in IQ scores in children of women with hypothyroidism at 4 years of age irrespective of whether they received thyroid supplementation during pregnancy. These studies will encourage further discussion among those for and those against universal thyroid screening in pregnancy. Randomized, controlled studies are urgently needed in order to guide physicians concerning when and how (which thyroid tests) to use to evaluate women of reproductive age and what is the proper medical management.

— Jorge H. Mestman, MD

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PROLONGED THERAPY WITH CARBIMAZOLE LEADS TO A 50% REMISSION RATE FOR GRAVES' DISEASE IN CHILDREN

Léger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C. **French Childhood Graves' Disease Study Group. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study.** J Clin Endocrinol Metab. October 26, 2011 [Epub ahead of print].

SUMMARY

BACKGROUND

The optimal therapy for Graves' disease in children is controversial. The remission rate with a single course of antithyroid drug is less than 30%. For this reason, many children are treated by either radiodiodine-131 (^{131}I) or surgical thyroidectomy as "definitive therapy." The policy for treatment varies among pediatric endocrinologists and institutions. The purpose of the current study was to assess the effect of the duration of carbimazole therapy on the remission of Graves' disease (GD) after three consecutive courses of carbimazole with discontinuation of the therapy after each course.

METHODS

This is a prospective study of 154 patients with GD up to age 18 in a multicenter French network. Each of the three treatment cycles with carbimazole lasted 2 years. The outcome after each course of carbimazole therapy was either relapse or remission based on follow-up for at least 18 months. If the patient relapsed, another course of therapy was begun, or if the patient and family preferred, definitive therapy was offered. Various demographic, clinical, and laboratory tests pertaining to thyroid function were performed. The variables associated with remission were analyzed with a regression model. These variables included age, sex, ethnicity, weight, height, body-mass index, pubertal stage, personal history of overt autoimmunity and susceptibility factors, family history of hyperthyroidism, severe initial clinical presentation, goiter, free thyroxine (T_4), free triiodothyronine, thyrotropin-receptor antibodies, and thyroid peroxidase autoantibodies.

RESULTS

The median duration of follow-up was 10.4 years. The mean age at presentation was about 12 years. Three serious adverse events occurred: allergic reaction, neutropenia, and arthralgia. The estimated remission rates 18 months after the withdrawal of antithyroid drug treatment increased with time and were 20% (95% confidence interval [CI], 13 to 26), 37% (95% CI, 29 to 45), 45% (95% CI, 35 to 54), and 49% (95% CI, 40 to 57%) after 4, 6, 8, and 10 years of follow-up, respectively. After 10 years follow-up, the estimated percentage of patients still receiving carbimazole was 11% and the percentage receiving definitive therapy was 36%. There was a positive effect on treatment of less severe forms of hyperthyroidism (free T_4, <35 pmol/L [2.7 ng/dl]). Age greater than 10 years at diagnosis was an independent predictor of definitive treatment (hazard ratio, 2.46; 95% CI, 1.12 to 5.40; P = 0.02). The presence of other autoimmune diseases increased the possibility of remission twofold but also predicted a longer duration of medical treatment.

CONCLUSIONS

About half the patients achieved remission after discontinuing carbimazole. There was a plateau in the incidence of remission achieved after 8 to 10 years of antithyroid drug therapy.

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ANALYSIS AND COMMENTARY

The best treatment of children with Graves' disease has been controversial for many years. The current study more or less confirms the findings reported from the UCLA Pediatric Endocrine Division in 1987; namely, that remission rates in children and adolescents treated with antithyroid drugs increased by 25% for every additional 2 years of treatment (1). The relatively low prevalence of Graves' disease in children, no more than 1 in 10,000 in the United States, makes it difficult to do randomized studies of different therapeutic regimens (3). Therefore, it is reassuring that this multicenter prospective study in France showed the efficacy of antithyroid drug therapy of children and reassured us that patience and a long-range outlook is a virtue in their treatment because remission increases with time. We now know that propylthiouracil is hazardous in this age group because it is associated with severe hepatotoxicity, but this does not occur with methimazole and presumably carbimazole that is converted into methimazole in vivo (2).

The high prevalence of 50% remission after 10 years of treatment found in this study is greater than the 15% to 30% remission reported in a recent review, although this lower percentage is consistent with 4 years of therapy (3). Although surgery has been recommended for children younger than 10 years of age, it has complications not found with radioiodine, such as hypoparathyroidism and recurrent laryngeal-nerve paralysis. Both of the definitive therapies usually cause permanent hypothyroidism, a complication not found with antithyroid drug therapy that usually leaves the thyroid gland intact. In fact, the pendulum has swung toward using a dose of ^{131}I that ablates the thyroid, even in children, leading to lifelong therapy with thyroid hormone (3), an outcome that I do not consider optimal.

— Jerome M. Hershman, MD

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TWO COMMONLY AVAILABLE "THIRD GENERATION" ASSAYS FOR ANTIBODIES TO THE TSH RECEPTOR (TSHR) ARE SIMILAR IN SENSITIVITY AND SPECIFICITY, BUT DIFFER IN THEIR RESPONSE TO SERA CONTAINING TSHR-BLOCKING IGGS

Kamijo K, Murayama H, Uzu T, Togashi K, Olivo PD, Kahaly GJ. **Similar clinical performance of a novel chimeric thyroid-stimulating hormone receptor bioassay and an automated thyroid-stimulating hormone receptor binding assay in Graves' disease.** Thyroid 2011;21:1295-1299. E-pub November 8, 2011; doi: 10.1089/thy.2011.0056.

SUMMARY

BACKGROUND

How antibodies activate the thyroid-stimulating hormone receptor (TSHR) remains controversial, but it is clear that immunoglobulins that bind to the TSHR and that stimulate adenylate cyclase can be found in the serum of most patients with untreated Graves' disease. This article compared two widely available "third generation" assays for measuring TSHR antibodies. The first assay measures the ability of a patient's serum to stimulate cyclic adenosine monophosphate (cAMP) production in cells transfected to express a synthetic mutant of the human TSHR (two authors are affiliated with the company that markets this assay). The other assay measures the ability of a patient's serum to inhibit the binding of a TSHR-stimulating antibody to an extract of porcine thyroid membranes. However, there are also TSHR-blocking antibodies in some patients with Graves' disease. How they block the responses of adenylate cyclase is poorly understood, and they are difficult to measure, but their clinical effects can confound an endocrinologist.

METHODS

The Thyretain assay (Diagnostic Hybrids) uses cultured Chinese hamster ovary (CHO) cells that stably express a genetically engineered human TSHR called "Mc4" (residues 262–335 in the C-terminal region of the extracellular domain of human TSHR were replaced with that region of the rat luteinizing hormone (LH) receptor, which theoretically eliminates epitopes that can be targets for some TSHR-blocking antibodies). When a serum sample that contains a stimulatory TSHR antibody is added to these cells, it activates the TSHR, causing light to be produced from luciferase, whose gene's promoter contains a cAMP regulatory element.

The Elecsys TRAb M22 assay (Roche) uses a detergent extract of porcine thyroid membranes stabilized by a biotinylated mouse monoclonal TSHR capture antibody, to which a patient's serum is added. Then M22, a human monoclonal antibody to the TSHR that is ruthenium-labeled, is added as a competitor for the porcine TSHR, along with streptavidin-bearing magnetic particles. The whole complex is captured on an electrode, and after washing, a voltage is applied that causes the ruthenium trapped in the complex to chemiluminesce, and the light is measured in a luminometer.

Sera from 106 patients with untreated Graves' disease, from 80 patients with autoimmune painless thyroiditis who were transiently hyperthyroid, and from 110 normal controls were tested using the two assays. Each patient with Graves' disease had to have a positive result on a screening Elecsys TRAb M22 assay, while each patient with painless thyroiditis had to have a negative result.

In order to be included, patients with Graves' disease also had to have laboratory results showing hyperthyroidism, a diffusely enlarged goiter, as well as a diffuse uptake of technetium-99m (99mTc) of >2.0% at 20 minutes and/or an increased "vascularity index" (>80%) on power color Doppler ultrasonography. [The vascularity index is the ratio of the number of color pixels to the total number of pixels in a 2-cm-by-2-cm square on the transverse scan of the right lobe. The first author of the current

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article recently published data using this index to try to distinguish patients with untreated Graves' disease from patients with painless thyroiditis; about 15% of the values in one group overlapped the values in the other. (1)] The patients with autoimmune painless thyroiditis also had to have laboratory results showing hyperthyroidism (reflecting transient destruction of thyroid tissue), as well as decreased uptake of 99mTc (<0.5% at 20 minutes) and/or a decreased vascularity index (<50%).

The authors also studied TSHR-blocking sera obtained from 8 patients with Graves' disease who had spontaneously become hypothyroid. The IgG from these patients' sera suppressed production of cAMP in TSH-stimulated pig thyrocytes by >46% (controls were <22%). These 8 sera then were tested for activity in the M22 and Mc4 assays.

RESULTS

The two assays were statistically equivalent in detecting TSHR antibodies in these patients with Graves' disease, although 2 of the 106 Graves' sera were negative on both assays. There also were discordant results on 10 sera: 6 were positive only on the Mc4 assay, whereas 4 were positive only on the M22 assay (so the 6 who had lost M22 positivity were false negatives). Furthermore, there were 5 false positives in the 80 patients with painless thyroiditis: 4 on the Mc4 assay plus 1 on the M22 assay (even though all the patients with painless thyroiditis had to be negative on the screening test with the M22 assay).

In the study on the sera with TSHR-blocking activity, all eight were strongly positive on the M22 TSHR binding assay, whereas not one was positive on the Mc4 cAMP stimulation assay.

CONCLUSIONS

The Mc4 and the M22 assays had equally high sensitivity and specificity on this group of patients with untreated Graves' disease. If one accepts that the "correct answer" was a positive test, then combining the two assays reduced the number of false negatives to 2 of 106. False positive results occurred in 5 of 80 patients with painless thyroiditis.

The sera containing TSHR-blocking antibodies reacted in the M22 assay as if they were TSHR stimulatory antibodies, since they competed with the M22 for receptors on solubilized porcine thyrocyte membranes. In contrast, none of these sera caused cAMP production in the CHO cells expressing the mutant Mc4 human TSHR.

ANALYSIS AND COMMENTARY

The patients in this study were highly selected. One would hope for a future study that would compare the two tests prospectively on all patients with newly diagnosed hyperthyroidism and that would follow the patients longitudinally for years after therapy is completed. Knowing how TSHR-stimulating and TSHR-blocking antibody levels change over time, as well as the changes in other thyroid antibodies, in thyroid-function tests and in clinical responses such as the presence and severity of ophthalmopathy, would be important for understanding what TSHR antibodies actually do. Such a study would also provide data concerning possible changes in TSHR antibody levels during the clinical course of thyrotoxicosis due to nodular thyroid diseases and in patients with a spectrum of types of painless thyroiditis.

Although these two assays are now in widespread use, a clinician may find it hard to establish which method is actually being used: Current Procedural Terminology codes can be misleading, information provided in test descriptions can be vague, references are often antiquated, and the nomenclature given to

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the test seems to be any random combination of the abbreviations for thyrotropin, receptor, and antibody. Nonetheless, it is important to know which test is being performed in order to know what substances can interfere with the test results.

The M22 assay recognized the blocking antibodies as if they were thyroid-stimulating antibodies, whereas the Mc4 assay did not detect any activity. Interestingly, an abstract at the recent ATA meeting (which included two of the current article's authors), indicated that adding sera containing TSHR-blocking antibodies plus bovine TSH to Mc4-expressing CHO cells reduced the expected cAMP responses, whereas the cAMP response was augmented if TSH-stimulating antibodies were added along with the bovine TSH. This approach could become a way to measure both stimulating and blocking antibodies (2).

A new low-molecular-weight compound has just been reported that blocks the cAMP and phospholipase C responses to TSH, to M22, and to TSHR-stimulating IgG. However the compound does not substantially affect their binding to the TSHR (3). The compound also inhibited the cAMP responses in cells expressing a chimera bearing the N-terminal extracellular domain of the human LH receptor plus the transmembrane and intracellular domains of the human TSHR, whereas it was inactive on cells expressing the reverse construct. This compound may prove useful for exploring how TSHR-blocking and TSHR-stimulating antibodies act, and it even could become the basis of a new kind of therapy for Graves' hyperthyroidism and/or orbitopathy (3).

— Stephen W. Spaulding, MD

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CAN WE MEASURE EARLY CARDIAC DYSFUNCTION IN PATIENTS WITH TSH SUPPRESSION?

Taillard V, Sardinoux M, Oudot C, Fesler P, Rugale C, Raingeard I, Renard E, Ribstein J, du Cailar G. **Early detection of Isolated Left Ventricular Diastolic Dysfunction in High-Risk Differentiated Thyroid Carcinoma Patients on TSH-Suppressive Therapy.** Clin Endocrinol (Oxf) 2011;75:709-14.

SUMMARY

BACKGROUND

Much has been written about possible cardiac side effects and bone loss during suppressive thyroxine treatment. An abundant literature points to possible left ventricular hypertrophy, but there is controversy about the functional consequences of this finding, since the commonly used two-dimensional echocardiography has its limitations in correctly evaluating left ventricular function. Speckle tracking echocardiography (STE) is a new noninvasive development of cardiac echocardiography that provides important additional information about cardiac deformation during contraction and relaxation. STE allows better appreciation of thickening, shortening, and twisting of the ventricular wall during the cardiac cycle. In patients with borderline cardiac function, TSH suppression may represent a precipitating factor, and objective signs of early cardiac dysfunction may be clinically useful. The present study used STE to provide information on the long-term cardiac effects of borderline hyperthyroidism. Previously, such information could only be obtained by means of cardiac magnetic resonance imaging (MRI).

METHODS AND RESULTS

As compared with classical echocardiography, STE visualizes and quantifies left ventricular deformation and rotation during the cardiac cycle, a phenomenon named in technical terms "two-dimensional strain" (meaning cardiac torsion). STE is also called "strain rate imaging." In other words, STE is able to simultaneously evaluate radial, longitudinal, and circumferential cardiac planes. This allows calculation of sophisticated and useful parameters such as the (mean) velocity of the circumferential fiber shortening, transmitral inflow, and early and late atrial filling.

The study was performed in 24 patients. Thyroxine treatment lasted for approximately 36 months. Twenty patients with additional disorders such as diabetes, hypertension, or preexisting cardiac insufficiency were excluded. The 24 remaining patients formed a very homogeneous group with similar histories of progressive thyroid cancer. The main suppressive dose was 2.3 μg/kg/24 hr (160 μg for a 70-kg patient). Serum thyrotropin (TSH) was <0.1 mU/L but, free thyroxine (T_4) and free triiodothyronine (T_3) were in the upper normal range. The control group consisted of 20 age- and sex-matched euthyroid subjects.

The results of two-dimensional echocardiography did not reveal any differences in left ventricular mass, relative wall thickness, ejection fraction, and cardiac output between patients and control subjects. However, with STE, early diastolic velocity and longitudinal proto-diastolic strain were shown to be impaired. This difference was an independent correlate of longitudinal diastolic strain. Thus, with STE, left ventricular mass was found to be increased in T_4-treated subjects.

CONCLUSIONS

The patients did not suffer from clinically overt hyperthyroidism and did not present with clinical evidence of worsening of their cardiac function. Classical two-dimensional echocardiography did not reveal any abnormalities, contrasting with the findings with STE that indicated an impairment of left ventricular longitudinal elongation.

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ANALYSIS AND COMMENTARY

The authors stress the point that this rather small group of patients was relatively homogeneous in terms of thyroxine treatment and stability of the underlying thyroid cancer. During the observation period, no patient had recurrence of the disease. Patients with major interfering disorders were excluded.

Following the landmark articles by Sawin et al. (1) and later Osman et al. (2, 3) pointing to the increased risk for atrial fibrillation in patients with TSH suppression, many studies have been published indicating some minor but nevertheless possibly deleterious effects on cardiac function. Other authors did not confirm these findings. STE may end this controversy by demonstrating that both phases of the early diastolic period were impaired, thus indicating left ventricular diastolic dysfunction. This correlated with changes in left ventricular mass. STE has the advantage of being noninvasive. Moreover, it avoids irradiation and is not expensive. Thus, it compares favorably with cardiac MRI in several aspects.

For thyroidologists, it would be interesting to know whether these cardiac changes occur only after many months of treatment or in its early phase. In an individual patient, it will be particularly interesting to perform STE studies before, during, and after treatment. Depending on the results, the cardiac and thyroidal surveillance of a patient at risk may need to be changed. It is reassuring that the cardiac abnormalities are most often reversible (4, 5). Yet, long-term studies are not available, and this new technique may add valuable new information about this point (6).

— Albert G. Burger, MD

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Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION FOUNDED 1923

POSTPARTUM PSYCHOSIS IS MORE PREVALENT IN WOMEN WITH AUTOIMMUNE THYROID DISEASE

Bergink V, Kushner SA, Pop V, Kuijpens H, Lambregtse-van den Berg MP, Drexhage RC, Wiersinga W, Nolen WA and Drexhage HA. **Prevalence of autoimmune thyroid dysfunction in postpartum psychosis.** Br J Psychiatry 2011;198:264-8. Epub February 22, 2011.

SUMMARY

BACKGROUND

Postpartum psychosis is a life-threatening psychiatric emergency that occurs in 0.1% of women who have borne children, often without significant premorbid symptoms. The clinical symptoms include fluctuations in mood accompanied by delusions and hallucinations, as well as agitation, insomnia, and cognitive impairment. Patients often require urgent hospital admission because of thoughts of suicide and infanticide. Women with bipolar affective disorder are at high risk for postpartum psychosis; up to half of women with bipolar disorder relapse in the early postpartum period, often with psychotic symptoms. However, most patients with a postpartum psychosis have no history of psychiatric disorder. Although many studies have postulated an involvement of the immune and endocrine systems in the onset of postpartum psychosis, the specific etiologic factors have remained unknown. The aim of the authors was to examine the hypothesis that autoimmune thyroid dysfunction may be associated with the onset of postpartum psychosis.

METHODS

Between August 2005 and November 2008 the authors examined all patients referred to the mother and baby inpatient unit of the department of psychiatry at the Erasmus Medical Centre for evidence of postpartum psychosis using the Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Structured Clinical Interview (SCID). Of the 123 patients examined, 55 fulfilled the criteria for postpartum psychosis. Patients were excluded from the study because of previous psychiatric history or multiparity. Thirty-one consecutive primiparous women with no prior psychiatric history were selected for the study; 23 presented with manic psychosis, 5 had a mixed episode, and 3 presented with psychotic depression. Selection of the control group (n = 117) was based exclusively on primiparity, regardless of medical or psychiatric history; they were followed during pregnancy and the first year after delivery to determine the incidence of postpartum thyroid dysfunction and postpartum depression. Blood samples were obtained from all participants at 4 weeks and 9 months postpartum. Patients with postpartum psychosis had blood samples taken at various times over the 9-month study period, as clinically indicated. Thyroperoxidase antibody levels, thyrotropin, and free thyroxine levels were measured to assess clinical thyroid disease.

RESULTS

No difference was found in the frequency of cesarean section, rate of primigravidity, birth weight of the child, or incidence of preterm birth between cases and controls. None of the patients or controls had a history of thyroid or autoimmune disease. At 4 weeks postpartum, 5% of the control group had autoimmune thyroid disease (AITD), with no cases of clinical thyroid dysfunction. In contrast, 6 of 31 (19%) of the patients with postpartum psychosis met criteria for AITD on admission to the hospital, before the start of antipsychotic or lithium pharmacotherapy (odd ratio [OR], 4.44; 95% confidence interval [CI], 1.32 to 14.92); half of them also demonstrated clinical thyroid dysfunction at the time of admission to the hospital. The 9-month prevalence of AITD was significantly higher in women with postpartum psychosis, 9 of 31 (29%) versus 15 of 117 controls (13%) (OR, 2.78; 95% CI, 1.08 to 7.17). Patients with postpartum psychosis showed a significantly higher rate of progression from subclinical AITD to clinical thyroid dysfunction (log-rank

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P = 0.017). Specifically, of the 9 patients with AITD at the 9-month follow-up, 6 (67%) had overt thyroid dysfunction as compared with only 20% of the control group (OR, 8.00; 95% CI, 1.23 to 52.25). Notably, the 3 patients in whom AITD and clinical thyroid dysfunction developed during treatment with mood stabilizers were all taking lithium. In contrast, none of the 18 lithium-treated patients without AITD had clinical thyroid dysfunction.

CONCLUSIONS

Women with postpartum psychosis are at higher risk not only of AITD but also of clinical thyroid failure. These data implicate thyroid dysfunction as an important clinical outcome in patients with postpartum psychosis. Further, AITD represents a potentially strong etiologic factor for the development of postpartum psychosis. Therefore, screening for TPO antibodies is warranted in patients with postpartum psychosis.

ANALYSIS AND COMMENTARY

Postpartum AITD, defined as the presence of thyroid peroxidase (TPO) antibodies in the first year after delivery, is reported in 5% to 7% of the general population (1). Postpartum thyroid dysfunction is characterized by three well-defined clinical patterns, all of them self-limited in the vast majority of cases (2, 3): (a) an initial phase of hyperthyroidism in the first 3 months postpartum followed by a euthyroid phase; (b) an initial hyperthyroid phase, followed between 3 and 6 months postpartum by a hypothyroid phase with spontaneous resolution; or (c) an initial hypothyroid phase between 3 and 6 months after delivery followed by euthyroidism. In less than 5% of patients, hypothyroidism may be permanent; however, it is important to follow patients because permanent hypothyroidism occurred in 30% to 50% by 5 years after the initial episode (4, 5), a pattern similar to women in whom type 2 diabetes developed following the diagnosis of gestational diabetes mellitus. The link between postpartum depression and chronic thyroiditis has been reported in the past (6, 7), although no evidence for an increase of AITD in patients with a late onset (>4 weeks after delivery) presentation of postpartum psychosis was found in the only previous systematic study (8). In the present study, a careful evaluation of women (primigravida with no previous psychiatric history) in whom serious signs of psychosis, requiring antipsychotic therapy, developed early in the postpartum period, showed not only a significant presence of thyroid autoimmune disease but also thyroid dysfunction within 9 months postpartum. Only 3 of 31 patients presented with psychotic depression, the others with manic psychosis, requiring multiple drug therapy, including lithium. The authors emphasized that of the lithium-treated women, thyroid dysfunction developed only in those with positive TPO antibodies. The other important observation is the higher rate of development of thyroid dysfunction in women with psychosis, as compared to controls with AITD. No information is given about the course of thyroid dysfunction at 9 months postpartum. It would be of interest to know how many women had a spontaneous return to the euthyroid state, as commonly occurs in women with postpartum thyroid dysfunction. This is the first observational study of primiparous women with AITD and no previous psychiatric history, showing a high prevalence of first-onset postpartum psychosis, as compared with the general population; therefore, it is reasonable to consider a previous postpartum psychosis event, including depression, as an indication for thyroid screening in future pregnancies of such affected women. Whether early identification and treatment of thyroid autoimmune disease would change the course of the disease deserves further study.

— Jorge H. Mestman, MD

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Clinical THYROIDOLOGY
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ELASTOGRAPHY IS NOT CLINICALLY USEFUL FOR DIAGNOSIS OF MALIGNANCY IN CYTOLOGICALLY INDETERMINATE THYROID NODULES

Lippolis PV, Tognini S, Materazzi G, Polini A, Mancini R, Ambrosini CE, Dardano A, Basolo F, Seccia M, Miccoli P, Monzani F. **Is elastography actually useful in the presurgical selection of thyroid nodules with indeterminate cytology?** J Clin Endocrinol Metab 2011;96:E1826-30. Epub August, 24, 2011.

SUMMARY

BACKGROUND

When fine-needle aspiration biopsy of thyroid nodules is performed, approximately one fourth fall into the indeterminate classification. Some authorities recommend surgical removal of all indeterminate nodules, although only about 10% to 30% are malignant. Real-time elastography (RTE) has been proposed to improve the diagnosis of thyroid cancer before surgery. Thyroid cancers have a harder consistency than benign thyroid nodules; RTE is a technique that uses ultrasonography to provide an estimation of tissue stiffness by measuring the degree of elasticity under the application of external light force. The goal of the current study was determine the efficacy of RTE, as compared with conventional ultrasonography (US), for differentiating malignant from benign thyroid lesions in patients being operated on for nodules with indeterminate cytology.

METHODS

The study included 102 patients (69 women) with indeterminate cytology who had conventional US and RTE performed by a skilled operator in the same session. Elasticity was scored from 1 (elastic) to 4 (stiff). The median nodule diameter was 2.2 cm (range, 0.7 to 10).

RESULTS

All patients underwent surgery; 36 had a pathologic diagnosis of cancer (32 follicular variant of papillary thyroid cancer, 2 classic papillary, and 2 follicular carcinoma). The remaining 66 nodules were benign, with a final pathology of follicular adenoma in 64 and hyperplastic nodule in 2. The only ultrasound feature that was significantly associated with the diagnosis of cancer was microcalcification, and this was found in 56%. Thyroid cancer was detected in 50% of the nodules that scored 1 to 2 on RTE (good elasticity) and in 34% that scored 3 to 4 (stiff). Of the 36 patients with malignant nodules, 32 had RTE scores of 3 to 4. Although the sensitivity was 89%, the positive predictive value was only 34% and the negative predictive value was 50%.

CONCLUSIONS

The current study did not confirm the utility of RTE for the differential diagnosis of malignancy or benignity in thyroid nodules with indeterminate cytology.

ANALYSIS AND COMMENTARY

Investigators from Pisa, Italy, had previously reported that RTE was useful for making a diagnosis of malignancy in indeterminate nodules with a positive predictive value of 77% and a negative predictive value of 99% (1). The cause of the lack of confirmation of this result in the current study is unclear. The person performing RTE in this study was very experienced. Nevertheless, there is a considerable element of subjectivity in this method. To overcome the subjectivity, software has been developed for quantitative analysis of stiffness. One technique, called "shear wave elastography," may be more useful because it eliminates the operator-dependence of the procedure (2, reviewed in the January 2011 issue of *Clinical Thyroidology*). It is likely that the true utility of shear wave elastography for discrimination between benign and malignant nodules in the indeterminate category will require additional studies for validation.

— Jerome M. Hershman, MD

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Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION FOUNDED 1923

USE OF RADIOIODINE ABLATION FOR THYROID CANCER HAS INCREASED AND VARIES INEXPLICABLY AMONG HOSPITALS

Haymart MR, Banerjee M, Stewart AK, Koenig RJ, Birkmeyer JD, Griggs JJ. **Use of radioactive iodine for thyroid cancer.** JAMA 2011;306:721-8.

SUMMARY

BACKGROUND

Radioactive iodine-131 (^{131}I) has been administered after thyroidectomy for differentiated thyroid cancer for half a century to eliminate residual thyroid tissue and possible metastatic disease. After initial surgery, the indications for radioiodine ablation have not been rigidly defined, leading to considerable variability in its use. The purpose of this study was to determine possible change in practice patterns and the degree to which hospitals in the United States vary in their use of radioactive iodine ablation and the factors that contribute to these variations.

METHODS

The National Cancer Database tracks about 85% of all thyroid cancers in the United States. The study queried 314,039 patients with primary thyroid cancers between January 1990 and December 2008. Only the 189,219 patients with differentiated thyroid cancer who had undergone total thyroidectomy were selected for analysis of various risk factors. Factors that correlated with use of ^{131}I were evaluated in the 85,948 patients diagnosed between 2004 and 2008. Cancer programs fell into the following four categories: community hospitals, comprehensive community, teaching/research, and National Cancer Institute/National Comprehensive Cancer Network.

RESULTS

Between 1990 and 2008, the proportion of patients who received ^{131}I as adjuvant therapy after total thyroidectomy increased significantly (P<0.001). In 1990, 40.4% of patients received radioactive iodine; in 2008, 56.0% received it. The increased use occurred for both larger and smaller tumors.

For the 2004–2008 cases, younger age was associated with a twofold increased use of ^{131}I. There was less use for AJCC stage 1 as compared with stages 2 to 4. There was less use of ^{131}I adjuvant therapy in hospitals with low case volumes (<7/yr) as compared with hospitals with high case volumes (>34/yr). For patients in the same risk category, there was wide variation between hospitals in the use of radioactive iodine. Patient and tumor variables were calculated to account for 21% of the variation in use of radioiodine ablation and unknown hospital factors for 29% of the variation.

CONCLUSIONS

The use of radioactive iodine ablation therapy increased between 1990 and 2008, and much of the variation in its use was associated with hospital characteristics.

ANALYSIS AND COMMENTARY

The large variation in use of radioactive iodine ablation among hospitals does not surprise me. I have noted through the years that the use of this therapy is based on local preferences, often those of hospital nuclear medicine departments, with some being much more aggressive than others. Although the study confirms that ablation therapy was used more with higher stages of cancer, it is startling that it was used more with younger rather than older patients, since older patients tend to have more aggressive and recurrent tumors. The increased use of radioiodine ablation in the period 1990–2008 probably reflects that its use became the "standard of care," despite a lack of controlled studies. The 2009 ATA guideline is to use radioiodine ablation in only select cases of stage

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1 disease, especially those with multifocal disease, nodal metastases, extrathyroidal or vascular invasion, and/or more aggressive histologies (1). Therefore, avoidance of radioiodine ablation in patients with tumors <2 cm and no other risk factors may reverse the trend of increased use, especially as more small tumors are being diagnosed and removed. In addition, there is increasing concern about the side effects of this therapy that include damage to the salivary glands and nasolacrimal ducts and secondary cancers, although these side effects are generally dose-related. These unfortunate consequences can be avoided with a return to the lower doses, such as 50 or 60 mCi, that were previously used for ablation therapy and that have been shown to be as effective as 100 mCi (2, 3). It is also important to note that a recent review did not find a statistically significant improvement in mortality or disease-specific survival in low-risk patients treated with radioiodine ablation (4).

It should be noted that this study was criticized because there was incomplete knowledge about how and why care was delivered in hospitals showing variation (5). If radioiodine ablation was not given to high-risk patients, the reasons it was not administered (such as patient preferences) were not captured in the database. If radioiodine ablation was given to low-risk patients, subtle information regarding a clinician's decision to administer radioactive ^{131}I is not captured in these databases.

— Jerome M. Hershman, MD

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AMERICAN THYROID ASSOCIATION
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Call for Proposals – American Thyroid Association (ATA) Research Grants -- Deadline: January 31, 2012

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

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 Development and the Brain. Research awards are intended to assist new investigators in obtaining preliminary data for submission of a more substantial application (i.e., to the NIH). Research grants, up to $25,000 annually, will be awarded for two year terms based 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 (i.e., to the NIH). Interested investigators should submit a brief description of the proposed research by January 31, 2012.

Eligibility of Applicant and Use of Funds Guidelines:

a. New investigators are individuals who are less than 6 years from completion of their post-doctoral fellowship and have never been a PI on an NIH RO1 or equivalent grant (recipients of NIH R29, R21 and KO8 awards are eligible).
b. Faculty members (MD and PhD) are eligible; however, those investigators who have reached the rank of associate professor or higher are not eligible.
c. 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.
d. Students working towards an MD or a PhD are not eligible.
e. Investigators and individuals who have previously received ATA, ThyCa or THANC awards are not eligible.
f. Applications are limited to one per individual researcher.
g. 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.
h. Recipients of ATA grants must be ATA members (submit application online if not already a member). For new members, membership dues for the first year will be waived.

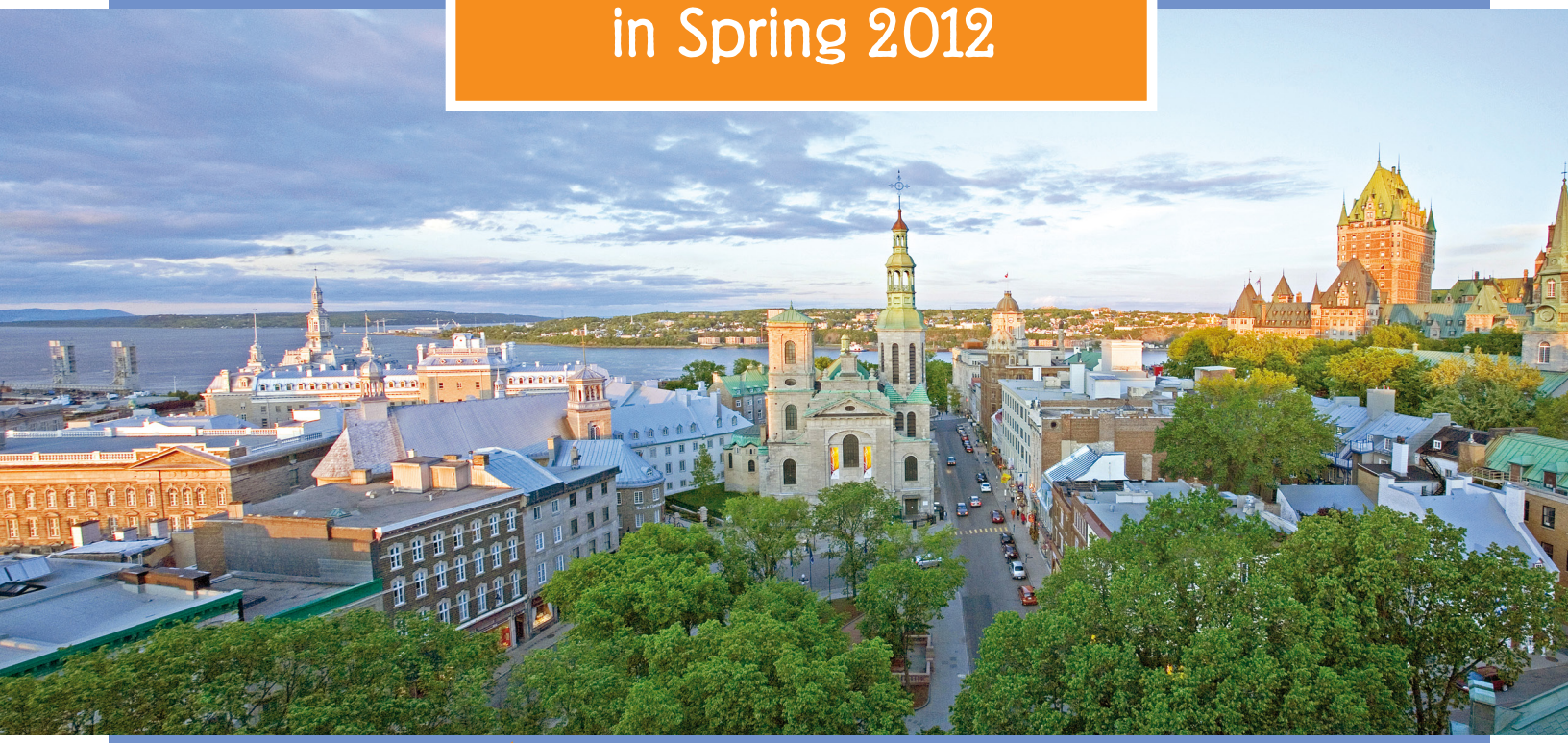
Proposal Requirements (please submit the following documents online):

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 **s**hort 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)

   a. 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 from the department chair must be provided that the applicant will have a junior faculty position at the time of the award. **Note: Without a suitable CV, applications will not be considered.**
3. Cover letter

Grant Review: The ATA Research Committee will rank proposals according to their scientific merit. Authors of selected proposals will be notified in March 2012 and invited to submit a complete grant application.

Registration Opening in Spring 2012



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

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