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PERSPECTIVE

PROPYLTHIOURACIL IS AN OLD BUT STILL USEFUL DRUG

Propylthiouracil (6-propyl-2-thiouracil, PTU) is probably one of the oldest drugs on the market in the Western world. Its use as an antithyroid drug has been well established for nearly 70 years (1). It was originally developed in the search for taste-changing substances (2). Its goitrogenic effect in laboratory animals led to the detection of its antithyroid effect. In the United States it is currently used as a second-line agent for control of hyperthyroidism and as a first-line agent in pregnancy and routinely by some practitioners.

PTU is rapidly absorbed from the gastrointestinal tract, peaking in serum within 1 to 2 hours after drug ingestion. Its half-life in serum is 75 minutes. Approximately 75% of PTU is bound to albumin. Serum levels have, however, little to do with its antithyroid effect, which typically lasts from 12 to 24 hours. PTU is actively transported into the thyroid, where it inhibits both the organification of iodine into tyrosine residues in thyroglobulin and the coupling of iodotyrosines. In contrast to methimazole (MMI), it has an important extrathyroidal action: it inhibits peripheral conversion of thyroxine (T_4) into the biologically more active (3,5,3¢-triiodothyronine (T_3) by inhibiting the enzyme 5 ¢-deiodinase type 1.

The pharmacokinetics are not altered in patients with hyperthyroidism or in chronic renal failure (3). They are, however, strongly influenced by iodine. In the presence of low intrathyroidal iodine concentration, PTU and/or its metabolites remain in the thyroid for a much longer time than in serum. With an iodide load (and high intrathyroidal iodine concentrations), PTU is more rapidly metabolized, and during long-term iodine contamination its uptake is also decreased (4). Patients with iodine-induced hyperthyroidism therefore need higher doses to control their thyrotoxicosis.

PTU like MMI, can cause rash, urticaria, arthralgias, arthritis, fever, nausea, or vomiting in approximately 14 to 20% of patients (3). PTU can also leave a bitter or metallic taste. Most of these side effects are considered to be allergic reactions. In one large study, the median duration of these side effects was 1.5 months. They were mostly controllable so that treatment could be continued in half of the affected patients, although at a lower dose (5). If one drug is not tolerated, then it can usually be substituted by the other drug. Some patients, however, experience cross-reactivity.

More severe, sometimes life-threatening, side effects such as agranulocytosis and hepatotoxicity were reported more than 60 years ago (6). Agranulocytosis

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is a rare but serious complication of treatment with PTU as well as with MMI. Its prevalence in patients treated with PTU is in the range of 0.1 to 0.5%. The prevalence seems to be independent of the age of the patient and of the dose used (3). Most—but by far not all—cases of agranulocytosis occur within 3 months after starting treatment. The utility of monitoring the white-count regularly during treatment has been challenged because of the usually very sudden onset of PTU-induced agranulocytosis. Patients taking PTU in whom fever or a sore throat develops should, however, immediately have a white-cell count with differential and discontinue the medication until the result is available. Recovery from agranulocytosis usually takes a few days, but morbidity and death from serious infections can occur, especially if agranulocytosis is prolonged (7).

Hepatic toxicity is also a rare, but especially in PTU-treated patients, sometimes life-threatening complication of thionamide therapy. This well-known phenomenon has recently raised much concern in the United States. PTU-induced hepatitis was first reported 4 years after the introduction of PTU (6). The results of baseline liver-function tests are, however, often abnormal in hyperthyroidism, and have not been found to be predictive for PTU-associated hepatotoxicity. Transient elevations in transaminases may occur during the first 2 months in up to one third of patients taking PTU and usually resolve with no intervention.

The first case of fulminant hepatic failure attributed to PTU was reported in 1953 by Eisen (8). Today, severe PTU-induced hepatotoxicity is postulated to be a dose-independent, idiosyncratic hypersensitivity reaction. It can occur any time over the course of therapy. The onset is sudden and the course is rapidly progressive. Its estimated incidence seems to be less than 0.5% in 35 patients with PTU-induced severe hepatic failure well-documented in the literature (9). Based on the assumption that 15,000 adults are treated with PTU per year in the United States and that the incidence of PTU-induced severe liver injury is approximately 0.1%, it has been calculated that this complication will develop in 15 adults annually. Of these 15 adults 10% will progress to acute liver failure requiring liver transplantation. Therefore, one can estimate that 1 of 10,000 adult patients treated with PTU will have severe acute liver failure requiring transplantation. The situation seems to be even worse for children, which has raised concern; the calculated risk to develop severe hepatotoxicity is in the range of 1 of 2000 children treated with PTU. This calculation is essentially based on data provided by the United Network for Organ Sharing (UNOS). These data from the United States, unfortunately, cannot be compared with data from Europe, since the European Liver Transplant Registry (ELTR) does not specify routinely which drug—except for acetaminophen—is responsible for their cases of drug-induced hepatic failure requiring liver transplantation.

In view of the data presented above and the very small but possible risk of MMI-induced embryopathy, a Task Force of the American Thyroid Association together with the American Association of Clinical Endocrinologists and the Food and Drug Administration has recently published the following recommendations regarding the use of PTU (10): 1) PTU should not be prescribed as a first-line agent in children or adults; 2) PTU is recommended when an antithyroid drug is to be started during the first trimester of pregnancy (until more is known about possible teratogenic effects of MMI); 3) PTU is recommended in preference to MMI in life-threatening thyrotoxicosis because of its ability to inhibit peripheral conversion of T_4 to T_3; 4) PTU should be used in patients with adverse reactions to MMI other than agranulocytosis and for whom radioiodine or surgery are not treatment options; 5) routine monitoring of the white-cell count and of liver function is not useful but should be performed in symptomatic patients.

My personal additional recommendation is that PTU should be used in preference to MMI also in lactating mothers, since its secretion in the milk is less than that of MMI (11).

— Michael Weissel, MD
Medical Clinic III
Medical University of Vienna, AUSTRIA
michael.weissel@meduniwien.ac.at

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MODIFIED-RELEASE RECOMBINANT HUMAN TSH AUGMENTS THE EFFECT OF ^{131}I THERAPY IN BENIGN MULTINODULAR GOITER

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SUMMARY

BACKGROUND

Surgical thyroidectomy or radioiodine-131(^{131}I) are the treatments for multinodular goiters that cause compressive symptoms or cosmetic disfigurement. However, many multinodular goiters have a relatively low uptake of radioiodine, so that the dose of ^{131}I necessary for a good effect becomes very large. The purpose of this study was to determine whether modified recombinant thyrotropin (MRrhTSH) could be used to stimulate radioiodine uptake and result in an effective reduction of the goiter and an increase in the tracheal lumen.

METHODS

The criteria for inclusion in the study were a clinical diagnosis of multinodular goiter that was 40 to140 ml in size by ultrasound and palpation, normal total triiodothyronine (T_3) and thyroxine (T_4) levels, TSH that ranged from suppressed to the upper limit of normal, negative results on fine-needle aspiration for thyroid cancer, and a normal electrocardiogram. Thyroid volume was measured by computed tomography at baseline and repeated after ^{131}I therapy. Radioiodine uptake was measured at 24, 48, and 120 to 168 hours. The ^{131}I dose was calculated to deliver 100 Gy to the thyroid gland. Patients were randomly assigned to receive either placebo, 0.01 mg of MRrhTSH, or 0.03 mg of MRrhTSH 1 day before the dose of ^{131}I was administered. MRrhTSH contains the same active ingredient as rhTSH (Thyrogen) but is reconstituted in a different diluent (sodium carboxymethylcellulose) to provide a delayed maximum concentration. The study was an international phase 2 trial sponsored by Genzyme (Cambridge, MA). Free T_4, free T_4 index, total T_4, free T_3, total T_3, and TSH were measured on days 2, 5, 14, 30, 60, and 180. A thyroid quality-of-life questionnaire was performed at baseline and on days 5, 90, and 180.

RESULTS

Ninety-five patients were selected for the study: 32 in the placebo group, 30 in the 0.01-mg MRrhTSH group, and 33 in the 0.03 -mg MRrhTSH group. The ages ranged from 35 to 80 years. Serum TSH ranged from undetectable to the upper limit of normal. The mean 24-hour thyroid uptake was approximately 30% and did not differ among the three groups. The mean doses of ^{131}I varied ranged from 32 to 39 mCi, with

TABLE 1. Changes in Goiter Volume (GV) Comparing the Initial Volume and the Volume 6 Months after ^{131}I Therapy.*

Treatment	Initial GV (ml)	GV at 6 mo (ml)	% Reduction in GV	>28% Reduction in GV
Placebo	100±45	77±37	23±9	25%
0.01 mg of MRrhTSH	93±51	70±36	23±16	37%
0.03 mg of MRrhTSH	103±39	70±37	33±21	64%

*Values are means ±SD.

a range of 5 to 103 mCi. Table 1 shows the results of the study in regard to the reduction of goiter size. The 0.03-mg dose of MRrhTSH caused a greater percent reduction in goiter volume than occurred with the placebo or the 0.01-mg dose. A clinically significant response was defined as a 28% or greater reduction in goiter size based on the literature. This was achieved in a significantly higher percentage (64%) of patients receiving the 0.03-mg as dose compared with the other groups. The smallest cross section of the trachea increased in all groups, and the increase did not differ significantly between the groups.

The majority of patients became either subclinically hyperthyroid or overtly hyperthyroid during days 1 to 20 after the ^{131}I therapy, but there was no difference between groups. Overt hypothyroidism at day 180 was most common in the high-dose MRrhTSH group (24%) as compared with either placebo (6%) or the low-dose MRrhTSH (3%) group. Every subject reported improved quality of life relative to baseline, but there was no difference between groups. Adverse events related to increased thyroid hormone levels and hyperthyroidism were more common in the groups receiving MRrhTSH. Atrial fibrillation developed in one patient 15 days later. Transient neck pain was reported in the placebo (9.4%), low-dose MRrhTSH (10%), and high-dose MRrhTSH (18.1%) groups.

CONCLUSION

The dose of 0.03 mg of MRrhTSH significantly augmented the effect of ^{131}I on reduction of the volume of multinodular goiters.

COMMENTARY 1

In the United States, the preferred treatment is surgery for large compressive goiters with ^{131}I treatment as the alternative (1). There are several single-institution trials demonstrating that pretreatment with rhTSH improved goiter shrinkage (1-5). Considering the high cost for thyroidectomy, including the risk of thyroid hormone replacement (100%), hypoparathyroidism (0.5 to 2%), and recurrent laryngeal-nerve damage (0.5 to 2%) in the hands of an experienced thyroid surgeon, rhTSH-stimulated ablation should be considered a cost-effective, viable option, since the majority of patients do not become hypothyroid and there is no risk to the parathyroid glands and the recurrent laryngeal nerves. When MRrhTSH becomes available, this therapy should be considered as first-line alternative treatment for large nontoxic goiters. This international study suggests that the response to rhTSH-stimulated ablation is similar in patients from different genetic backgrounds and with different iodine intake in different countries. Nevertheless, my first choice will remain surgery for the large symptomatic nontoxic goiter, but I will look forward to additional trials for this new form of rhTSH.

— Stephanie L. Lee, MD, PhD

COMMENTARY 2

Since Huysmans pioneered the use of rhTSH to increase thyroid uptake of radioiodine, several groups have used rhTSH in single doses that range from 0.03 to 0.45 mg to increase the thyroid uptake of a therapeutic dose of radioiodine-131 in patients with nodular goiter in order to reduce goiter size and compressive symptoms (1-8). A dose of 0.03 mg of ordinary rhTSH resulted in similar goiter volume reduction and increase of the tracheal lumen that were achieved with 0.03 mg MRrhTSH (6). One side effect of this therapy for multinodular goiter is the development of Graves' hyperthyroidism in some patients (2).

I have used 0.1 mg of rhTSH to increase thyroid uptake of a therapeutic dose of ^{131}I in patients with subclinical hyperthyroidism and relatively low 24-hour radioiodine uptake. In general, the rhTSH causes a doubling of the 24-hour uptake of radioiodine, thus enabling the administration of a lower total dose of ^{131}I.

A study of the stability of rhTSH in regard to stimulating the uptake of radioiodine in cultured thyroid cells showed that rhTSH kept at 4°C, –11°C, –60°C, and room temperature maintained good biologic potency for more than 6 months of storage, indicating that the biologic activity is very stable (9). Recombinant TSH is provided in ampules containing 1.2 mg. If the material is allocated by your pharmacy into various vials after dilution and stored in the cold, it could be sufficient for treatment of many patients with multinodular goiter over a 6-month period. Lastly, it should be noted that this treatment of multinodular goiter is an off-label use of rhTSH.

— Jerome M. Hershman, MD

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IS OBESITY DIRECTLY INVOLVED IN CAUSING THYROID CANCER?

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SUMMARY

BACKGROUND

Both thyroid cancer and obesity are increasing in the general population, but are the two connected?

METHODS

The statistical connection between body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) and thyroid cancer was analyzed using the data from five prospective U.S. National Cancer Institute studies that were performed over various periods between 1979 and 2009 (mean follow-up, 10 years). Baseline questionnaires from approximately 414,000 women and 435,000 men provided data on demographics, lifestyle, and medical history. Participants' height and weight were measured in one study, whereas this information was self-reported in four. Cancer information was obtained from self-reports (three studies), cancer registry linkage (four), death certificates (three) and/or the National Death Index (four). The type of thyroid cancer was established from clinical and pathology records, and cancer registry linkage. Of 1156 participants diagnosed with a malignant first primary thyroid neoplasm, histologic data were available on 1024 (80% were papillary, 15% follicular, 3% medullary, and 2% anaplastic). The mean age at study entry was 58 years, and 20% of participants were obese. Data were adjusted for education, race, marital status, cigarette smoking, alcohol intake, physical activity, and sex. There was no significant heterogeneity between the studies. Participant data were collected up to the first diagnosis of any cancer (other than nonmelanoma skin cancer), death, or the last questionnaire completed.

RESULTS

When BMI was modeled as a continuous variable, and data from men and women were combined, the relationship between BMI and thyroid cancer was log-linear. The hazard ratio (HR) was 1.17 and the 95% confidence interval (CI) was 1.10 to 1.24. When participants' BMIs were segregated into normal (18.5 to 24.9), overweight (25.0 to 29.9) or obese (>30), the HR was 1.20 for overweight (95% CI, 1.04 to 1.38) and 1.53 for obesity (95% CI, 1.31 to 1.79) (approximately 3000 individuals were excluded from analysis because of a BMI <15 or >50). There was no significant difference between histologic types, and no modification by other factors.

When the data were examined for each sex separately, thyroid cancer was associated with a high BMI in two of four studies for men (not significant) and four of five studies for women (HR, 1.16). However, if the first 2 years of follow-up were excluded to eliminate bias from participants who might have had preclinical disease at baseline—and thus whose weight might have changed as a result of the disease—the hazard ratio became significant for men as well as women.

CONCLUSIONS

This pooled analysis supports previous findings that obesity is a significant independent risk factor for thyroid cancer in both sexes.

COMMENTARY

There could be a specific detection bias if obese patients had more frequent or more thorough examination of their thyroids, along with assessment of their thyroid function. Contrariwise, self-reported weight is often underestimated while height is overestimated, factors that might have biased the study against what was actually found. Various mechanisms have been suggested as possible connections between obesity and carcinogenesis. From an endocrine viewpoint, obesity is associated with increased production of estrogen, insulin, insulin-like growth factor 1, adipokines, and inflammatory mediators. Many xenobiotics accumulate in adipose tissue and then are released over the long term; some can act directly as carcinogens by forming bulky DNA adducts that resist normal repair pathways, others activate pro-carcinogens via CYP- and aryl-hydrocarbon receptor-mediated pathways, and some alter the production of free radicals or have epigenetic effects.

If we were to begin a giant prospective epidemiologic study over 20 or 30 years, would it actually identify some of the factors related to obesity-related thyroid cancer? Maybe not, but if the incidence of thyroid cancer in the general public continues increasing at the rate observed over the past decade, even skinny people may wish there were such a study. Nonetheless, telling ourselves that obesity increases the risk of thyroid cancer developing by 50% probably will not motivate us to lose weight or to increase our awareness of the spectrum of xenobiotics that can be present in the American diet.

— Stephen W. Spaulding, MD

SUPPLEMENTATION OF METHIMAZOLE TREATMENT WITH MODERATE DOSES OF IODIDE (38 MG/DAY) QUICKLY IMPROVES HYPERTHYROIDISM

Takata K, Amino N, Kubota S, Sasaki I, Nishihara E, Kudo T, Ito M, Fukata S, Miyauchi A. **Benefit of short-term iodide supplementation to antithyroid drug treatment of thyrotoxicosis due to Graves' disease.** Clin Endocrinol (Oxf) 2010;72:845-50.

SUMMARY

BACKGROUND

Combining an antithyroid drug with high doses of potassium iodide (KI) is a well-established procedure to rapidly alleviate thyrotoxic symptoms in severely ill patients with Graves' disease who are scheduled for thyroid surgery. This method takes advantage of the inhibitory action of iodine not only on the synthesis of thyroid hormones, but also on their secretion. However, long-term treatment of Graves' disease with KI is not advisable because of the possible escape, the so-called Wolff–Chaikoff effect. It is only in patients who have undergone treatment with partly ablative doses of radioactive iodine (^{131}I) and in patients with hyperthyroidism who have been treated with ipodate that this rule does not apply. Yet, so far—with few exceptions—only the effect of very large doses of KI have been studied and most patients included in these studies were living in areas with low or moderate iodine intake. In the article under discussion, the effect of treatment of ordinary patients with Graves' disease with the combination of methimazole (MMI) and a relatively small dose of KI was studied in a Japanese population who did not have iodine deficiency.

METHODS

In this study, 162 patients with Graves' disease were initially selected; 134 successfully fulfilled the requirements of the protocol, which was designed to study the response of serum free thyroxine (T_4) and free triiodothyronine (T_3) to an MMI treatment with and without the addition of 38 mg iodide (50 mg of KI per tablet). Four similarly sized groups of patients matched for sex and age were prospectively studied. Group 1 received 30 mg of MMI; group 2 received in addition one tablet of KI; group 3 received only 15 mg of MMI, and group 4 received 15 mg of MMI plus one tablet of KI. This treatment schedule was maintained until the free T_4 decreased into the normal range. At this time (i.e., 2 to 8 weeks after the beginning of treatment), KI was stopped. Therefore, KI was given for only a rather short period. MMI treatment was maintained, adjusted, and then stopped when serum free T_4 and serum thyrotropin (TSH) were in the normal range for more than 6 months. Patients were considered to be in remission if, after this date, they remained euthyroid (normal free T_4 and normal serum TSH values) for 1 year.

RESULTS

Independent of the dose of MMI, the addition of KI resulted in a more rapid normalization of serum free T_4. With 30 mg of MMI plus KI, free T_4 normalized in 58% of the patients within 2 weeks, while with 15 mg of MMI, this result was achieved in 53% of the patients. At 4 weeks of treatment, the response was still in favor of those receiving KI, but the difference was no longer significant. After ending the KI treatment, there was transient, clinically irrelevant rebound of free T_4 and free T_3.

The percentage of remissions, defined as 1 year of treatment-free euthyroidism, was not different among the groups. There was a nonsignificant tendency for a higher remission rate in patients who had received the combined treatment.

CONCLUSION

Combined treatment with methimazole and potassium iodide improved the short-term control of hyperthyroidism and did not cause worsening hyperthyroidism when KI was stopped.

COMMENTARY

It is to be expected, as again confirmed here, that adding a supraphysiological dose of iodine to an antithyroid drug in order to achieve remission in patients with Graves' disease will result in a more efficient blockade of hormone secretion from the thyroid gland. The work of Takata et al. adds some valuable information about the dose–response relationship, the kinetics, and the late outcome of the combined treatment. While most (though not all) related studies used much higher iodine doses (mostly 250 to 500 mg iodine as Lugol's or supersaturated potassium iodide [SSKI] solution), only one tablet of 50 mg of KI containing 38 mg of iodine was used in this study (1,2). Nevertheless, most clinicians would probably have expected a more dramatic effect of the combined treatment than that observed in the study. Indeed, in the group receiving 30 mg of MMI, it was only at 2 weeks that free T_4 and free T_3 were significantly lower with added iodine than without it. In the group receiving 15 mg of MMI, a significant difference was also observed in the 4th week of treatment, suggesting that this dose of MMI does not achieve the same degree of thyroid blockade as does 30 mg of MMI. A very few patients were apparently more or less resistant to both forms of treatment, particularly when treated with 15 mg of MMI. Taken together with the all-important observation that the incidence, the quality, and the duration of long-term remission did not differ among patients given 30 mg of MMI alone or in combination with iodine, I conclude that the present work does not provide convincing evidence to suggest a compelling need to add iodine to MMI in ordinary patients with Graves' disease. It is, however, remarkable that stopping KI treatment did not result in relapses. The occasional use of KI may therefore be worthwhile in patients with adverse cutaneous reactions to high doses of MMI.

— Albert G. Burger, MD

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LEVOTHYROXINE INGESTION IN THE EVENING RESULTS IN BETTER ABSORPTION THAN INGESTION BEFORE BREAKFAST

Bolk N, Visser TJ, Nijman J, Jongste IJ, Tijssen JG, Berghout A. **Effects of evening vs morning levothyroxine intake: a randomized double-blind crossover trial.** Arch Intern Med 2010;170:1996-2003.

SUMMARY

BACKGROUND

Levothyroxine is usually taken in the morning on an empty stomach because food may interfere with its absorption. The purpose of this study was to determine whether taking levothyroxine at bedtime results in better absorption and improved clinical outcome than taking it before breakfast.

METHODS

This was a randomized double-blind crossover trial in which patients took a capsule of levothyroxine or placebo 30 minutes before breakfast or before sleep on an empty stomach. The patients were all on stable doses of levothyroxine for at least 6 months. Patients with thyroid cancer, gastrointestinal disorders that could alter thyroxine absorption, and medicines that could interfere with thyroxine absorption were excluded. The capsules were formulated from commercial levothyroxine sodium using lactose monohydrate as the excipient. Blood samples for measurement of thyrotropin (TSH), free thyroxine (T_4), total triiodothyronine (T_3), and lipids were obtained at baseline and every 6 weeks Patients were crossed over to the other time of ingestion at 12 weeks. The thyroid parameters were compared at the 12- and 24-week intervals for each mode of administration. Patients also completed questionnaires concerning general health, fatigue, and symptoms of thyroid dysfunction at baseline and at 12 and 24 weeks.

RESULTS

Of the 105 patients who entered the study, 90 completed it. The mean age was 48 years, the duration of hypothyroidism varied from 0.5 to 25 years, and the dose of levothyroxine varied from 50 to 250 µg with the median being 100 or 125 µg. Bedtime levothyroxine intake resulted in a decrease in TSH of 1.25 mIU/L (95% confidence interval [CI], 0.60 to 1.89; P_=0.001) relative to morning levothyroxine intake, an increase in free T_4 of 0.07 ng/dl (95% CI, 0.02 to 0.13; P = 0.01), and an increase in T_3 level of 6.5 ng/dl (95% CI, 9.0 to 12.10; P = 0.02). There were no differences between the two dosing regimens in quality of life, symptoms of fatigue, thyroid symptoms, or lipid levels. At 1 year after completion of the trial, a majority of the patients preferred the evening dose.

CONCLUSION

Ingestion of levothyroxine at bedtime resulted in better absorption than ingestion 30 minutes before breakfast.

COMMENTARY

The results of this study are consistent with anecdotal reports showing that absorption of levothyroxine is better, indicated by a lower TSH and higher free T_4 on the same dose, when the pill is taken at bedtime rather than before breakfast. However, another carefully performed study came up with the opposite result (1). In that study, breakfast was delayed for at least 60 minute before the ingestion of levothyroxine. Perhaps the interval of 30 minutes used in the study under discussion was too short to prevent food ingestion from interfering with levothyroxine absorption. However, there were differences in the study populations, such as inclusion of thyroid cancer patients in the study by Bach-Huynh et al (1).

In a number of my patients who had otherwise unexplained fluctuating serum TSH levels on the same dose of levothyroxine when they took it before breakfast, I found that changing the dose to bedtime resulted in a more reliable serum TSH level. As someone who eats breakfast as soon as possible after arising, I can sympathize with patients who do not want to wait 1 hour before eating breakfast. Let me hear from you about your experience in regard to the optimal time for taking levothyroxine.

— Jerome M. Hershman, MD

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ULTRASONOGRAPHY MAY DETECT MALIGNANT NODULES IN PATIENTS WITH HASHIMOTO'S DISEASE

Mukasa K, Noh JY, Kunii Y, Matsumoto M, Sato S, Yasuda S, Suzuki M, Ito K, Ito K. **Prevalence of malignant tumors and adenomatous lesions detected by ultrasonographic screening in patients with autoimmune thyroid diseases.** Thyroid 2011;21:37-41. Epub October 9, 2010.

SUMMARY

BACKGROUND

There has been considerable controversy about whether autoimmune thyroid disease predisposes patients to papillary thyroid cancer. The purpose of the study was to determine the incidence of thyroid cancer in patients with Hashimoto's thyroiditis or Graves' disease.

METHODS

The authors performed thyroid ultrasonography to detect thyroid nodules in 2036 patients with Hashimoto's thyroiditis and 1652 patients with Graves' disease. If nodules larger than 1 cm and suspicious for a malignant tumor were found based on ultrasound criteria, ultrasound-guided fine-needle aspiration (FNA) biopsy was performed.

RESULTS

Thyroid nodules were found in 634 patients (31%) with Hashimoto's disease and in 294 (18%) with Graves' disease. FNA was carried out in 177 of the Hashimoto's group and in 50 of the Graves' patients. Thirty-eight of the patients with Hashimoto's disease (1.8%) had papillary cancer, and two had malignant lymphoma. Seventeen (1%) of the Graves' group had differentiated thyroid cancer. The remainder of the biopsies were adenomatous lesions.

CONCLUSIONS

The authors recommend performing ultrasonography at the time of the initial visit in patients with autoimmune thyroid disease to detect malignant thyroid tumors.

COMMENTARY

There have been many reports about the coexistence of papillary thyroid cancer and Graves' disease when patients were treated with surgical thyroidectomy and the resected gland was studied carefully. The thyroid-stimulating IgG has been thought to play a role in stimulating growth of the tumor cells. Since Graves' disease is rarely treated by surgery in the United States currently, the finding of incidental thyroid carcinomas is now rare.

This article is most interesting in regard to finding a 1.8% incidence of papillary thyroid cancer in patients with Hashimoto's disease. This comprised 5.7% of the biopsies, a figure very similar to the incidence of malignancy found in many early FNA reports (1) and less than the figure of 10% or higher noted in more recent reports (2). A recent prospective study in Turkey found that only 2 of 191 patients with Hashimoto's disease with nodules had thyroid cancer, as compared with 19 of 713 nodules in a control (no Hashimoto's disease) group, the difference being not significant (3). However, there continue to be publications, usually retrospective surgical series, claiming that Hashimoto's disease is a risk factor for papillary thyroid cancer (4).

Despite this long-standing controversy concerning whether Hashimoto's thyroiditis predisposes to thyroid neoplasia, I generally tell my patients that Hashimoto's disease does not predispose to thyroid cancer (aside from the rare lymphoma), but that distinct nodules found on ultrasound have to be evaluated in a conventional manner. On ultrasonography, many of these lumpy Hashimoto's glands are diffusely sonolucent and have no distinct worrisome nodules, making it reasonable to reassure the patient that there is no evidence of malignancy.

— Jerome M. Hershman, MD

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PROGRESSION FROM EUTHYROID AUTOIMMUNE DISEASE TO CLINICAL DISEASE: HOW OFTEN, HOW SOON?

Effraimidis G, Strieder TG, Tijssen JG, Wiersinga WM. **Natural history of the transition from euthyroidism to overt autoimmune hypo- or hyperthyroidism: a prospective study.** Eur J Endocrinol 2011;164:107-113. Epub October 18, 2010.

SUMMARY

BACKGROUND

The purpose of the study was to evaluate in a prospective manner the progression from euthyroidism to overt autoimmune hypothyroidism or hyperthyroidism and to examine the involvement of certain environmental factors in the development of events.

METHODS

The prospective Amsterdam autoimmune thyroid disease (AITD) cohort consisted of 803 female subjects between 18 and 65 years of age, with no history of thyroid disease, who were in self-proclaimed good health and had at least one first- or second-degree relative with documented AITD. At entry into the study, 13 participants were diagnosed with active disease and excluded, leaving 790 women for follow-up. They were seen every year during a 5-year period.

Subjects received yearly thyroid tests and were asked to fill in questionnaires on smoking habits, pregnancy, estrogen treatment, and iodine excess in the previous year. End points of the study were either completion of the 5-year follow-up or the development of overt hypothyroidism or hyperthyroidism.

Hypothyroidism developed in 38 women (4.8%), 34 with Hashimoto's disease and 4 with postpartum thyroiditis, and hyperthyroidism developed in 13 (1.6%), 11 with Graves' disease, 1 with postpartum thyroiditis, and 1 with silent thyroiditis. For each of these 51 patients, 2 controls were selected from the remaining subjects, matched by age at study entrance, and the analysis of their data was limited to the same visit at which the case patients had reached their end point, thereby controlling for exposure to environmental factors for precisely the same follow-up period.

RESULTS

The average period between study entrance and the occurrence of an event was 3 years. At baseline, the 38 patients with hypothyroidism already had higher thyrotropin (TSH), lower free thyroxine (T_4) and higher thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibody (TgAb) serum concentrations than their 76 age-matched controls, and the difference between the two groups persisted at 1 year before occurrence of the event. At baseline, 7 of the 38 women in whom hypothyroidism developed had subclinical hypothyroidism; excluding these 7 patients did not alter the results.

In the 13 patients with hyperthyroidism, neither TSH nor free T_4 values differed between patients and controls at baseline or at 1 year before the event, but the prevalence and the titers of antibodies was higher in patients than in controls. At baseline, 2 subjects had subclinical hyperthyroidism, but as in the women with hypothyroidism, excluding these two patients from the analysis did not alter the results.

The difference in TPOAb and TgAb concentrations was not significant between patients with hypothyroidism and those with hyperthyroidism, neither at baseline nor at 1 year before occurrence of the event.

Smoking status was similar in controls and patients at entrance and at 1 year. However, there were fewer current smokers among patients with hypothyroidism than among controls (13% vs. 28%, P = 0.083).

However, there were more cases of postpartum hypothyroidism in the patients than in the controls (8 of 38 [21%] vs. 3 of 76 [4%], P = 0.006). Postpartum hyperthyroidism developed in 2 of 13 (15%) patients versus 1 of 26 (4%) controls (P = 0.06).

The use of oral estrogens did not differ between patients and control at any time.

CONCLUSIONS

The data suggest that progression toward overt autoimmune hypothyroidism is a gradual process taking several years, but overt autoimmune hyperthyroidism develops much faster.

COMMENTARY

The authors confirmed previous studies (1,2) showing the predictive value of mild elevations of serum TSH and the presence of positive thyroid antibodies in the future development of clinical hypothyroidism and suggested that progression toward overt autoimmune hypothyroidism is a gradual process, taking several years. In the Whickham (3) survey , the annual rate of progression from subclinical to overt hypothyroidism was 3% in women with elevated TSH values (> 6mU/L), 2% in women with positive antibodies, and 4.3% in the presence of an elevation of both serum TSH and TPOAb.

Effraimidis et al. studied a selected population of euthyroid women, ages 18 to 65, with a family history of thyroid disease. Within 5 years after the initial examination, 38 of 790 women (4.8%) had overt hypothyroidism; 7 of them already had subclinical hypothyroidism at entrance to the study. We do not know for how long their serum TSH was in the upper limit of normal and for how long they had positive antibodies. Interestingly, the episodes of postpartum thyroiditis were similar in patients and controls at study entrance.

For the 13 women (1.3%) in whom hyperthyroidism developed, the only significant difference between the groups was the higher incidence and higher TPOAb titers in patient versus controls, both at entrance to the study and at 1 year before occurrence of the event. Two of 13 in the hyperthyroid group already had subclinical disease at entrance. The authors did not state the time elapsed for hyperthyroidism developing in the 2 patients with subclinical hyperthyroidism at study entry. At study entry, in the patients with hypothyroidism, serum TSH and TPOAb concentrations were higher and serum free T_4 levels were lower than in controls.

In contrast, baseline serum TSH and free T_4 concentrations were not different between patients with hyperthyroidism and controls, and this was still true 1 year before the occurrence of the event, suggesting that the transition from euthyroidism to overt autoimmune hyperthyroidism develops quickly, in months rather than years. The authors mentioned their own previous study, in which the duration from Graves' disease symptoms until diagnosis was 4 months.

Several environmental factors were studied in this particular population. Smoking status did not differ between patients and controls at baseline or 1 year before the event. The proportion of current smokers was lower in the patients with hypothyroidism than in controls, but only at the time of the event, although it was of marginal statistical significance (P = 0.08).

Recent reports cited by the authors showed that smoking protects against the development of TPOAb and also against the development of hypothyroidism. No difference was found in the influence of smoking between patients with hyperthyroidism versus controls.

Pregnancy was a factor in both patients with hyperthyroidism and those with hypothyroidism. Postpartum thyroiditis was significantly higher in hypothyroidism than in controls, but was not statistically significant in the patients with hyperthyroidism versus the controls (P = 0.06).

The strength of the study is its prospective nature, with annual assessments during 5 years of follow-up in a selected population; the authors stated that they are not aware of studies assessing the transition from euthyroidism to overt autoimmune hypothyroidism or hyperthyroidism in a structured, prospective manner.

The authors proposed a model for the natural history of AITD, arising from the interplay between a particular genetic background involving multiple genes, accounting for 70% of the risk of AITD and a variety of environmental factors, accounting for about 30% of the risk. Smoking and a low iodine intake favor development of hyperthyroidism, whereas not smoking and a high iodine intake favor development of hypothyroidism. The transition from euthyroidism to overt hyperthyroidism occurs in months, provoked, for example, by stress and pregnancy, whereas the transition from euthyroidism to overt hypothyroidism may take several years, triggered by pregnancy (postpartum period) and by quitting smoking.

The dilemma for practicing endocrinologists from this and previous studies on the management of subclinical hypothyroidism is if and when thyroid therapy is indicated, since the vast majority of patients are asymptomatic. The recommendations suggested in the literature are controversial (4), because there are no robust data favoring T_4 therapy, with the exception perhaps of pregnancy or for women planning a pregnancy. If thyroid replacement therapy is not given, how often do these patients need to be tested?

Similar questions arise in the treatment of women with euthyroid chronic thyroiditis. There are no clear answers, but it would depend on several factors, among them age and planning a pregnancy.

— Jorge H. Mestman, MD

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CHILDREN WITH PRADER–WILLI SYNDROME FREQUENTLY HAVE CENTRAL HYPOTHYROIDISM

Vaiani E, Herzovich V, Chaler E, Chertkoff L, Rivarola MA, Torrado M, Belgorosky A. **Thyroid axis dysfunction in patients with Prader–Willi syndrome during the first 2 years of life.** Clin Endocrinol 2010;73:546-50.

SUMMARY

BACKGROUND

Prader–Willi syndrome is a rare genetic disease with an incidence of 1 in 10,000 to 1 in 16,000 newborns. The endocrine abnormalities show evidence of hypothalamic pituitary dysfunction, and magnetic resonance imaging occasionally shows pituitary hypoplasia, empty sella syndrome, and a small or absent posterior pituitary gland. Central hypothyroidism has been reported in 20% to 30% of patients. This study is a prospective investigation of thyroid function in all infants diagnosed at the Hospital de Pediatria Garraham in Buenos Aires over a period of 5 years.

METHODS

Eighteen patients (11 boys and 7 girls) up to 2 years of age were included in this prospective study. The diagnosis was documented by molecular biology, and mutations were identified in all cases. At birth, neonatal thyrotropin (TSH) screening was normal. The diagnosis was established as early as 1.9 months to 2 years postnatally. The presumptive diagnosis of thyroid dysfunction was based on serum TSH, triiodothyronine (T_3), thyroxine (T_4) and free T_4 levels. Their normal ranges were established specifically for the hospital laboratory. The values were considered pathological if serum free T_4 was less than the 2.5th percentile of the reference age-matched population and if there was absence of the expected increase in serum TSH. This definition of a possible thyrotropin-releasing hormone TRH/TSH dysfunction was based on international laboratory medicine recommendations. A T_4 below 2 SD was further indicative of hypothyroidism.

RESULTS

Mean length and weight at the time of diagnosis was slightly decreased as compared with the reference population. Four patients were small for gestational age and two were born prematurely. In 61% (11 of 18), free T_4 values were below the 2.5 percentile, and in two additional cases the value was just borderline. With the exception of one case, all patients had normal serum T_3 levels. Interestingly, body length was significantly shorter in the hypothyroid patients than in the small group of patients without thyroid dysfunction.

CONCLUSIONS

In Prader–Willi syndrome, the presence of TRH/TSH dysfunction is more frequent than had been reported earlier and is seen at a very early stage of life. At present, it is not clear whether this dysfunction is transient or permanent. It is suggested that this represents subclinical central hypothyroidism.

COMMENTARY

Prader–Willi syndrome is a genetic disorder. Patients with this disorder have moderate to severe mental retardation, hypotonia, and short stature. They rarely achieve coherent speech. Hyperphagia is a constant feature of the syndrome resulting in severe obesity. Puberty is retarded. Deficiency of luteinizing hormone, inhibin and increased follicle-stimulating hormone, a mixed form of central and peripheral hypogonadism, are part of the syndrome. It is suggested that the phenotype is secondary to hypothalamic dysfunction.

In the article under discussion, the authors consider their findings to be indicative of hypothalamic thyroid dysfunction. They do not use the term central hypothyroidism because despite the low free T_4/TSH ratio, serum T_3 levels were normal. The strength of the study is the large number of cases collected prospectively in one institution and the careful

establishment of an age-dependent reference range for the thyroid tests. Obviously, TRH testing would have been helpful, but the test is no longer available, although it was used in a limited number of cases reported earlier.

Patients with Prader–Willi syndrome benefit from growth hormone treatment in two ways: the treatment improves final height, but more importantly, it reduces severe obesity. The patients do not have an absence of growth hormone but only a partial deficiency. In view of the crucial role of thyroid hormones for early brain development, one can only agree with the authors, who raise the question of whether infants with Prader–Willi syndrome who have an abnormal free T_4/TSH ratio, but normal serum T_3 levels, will benefit from thyroid hormone treatment.

— Albert G. Burger, MD

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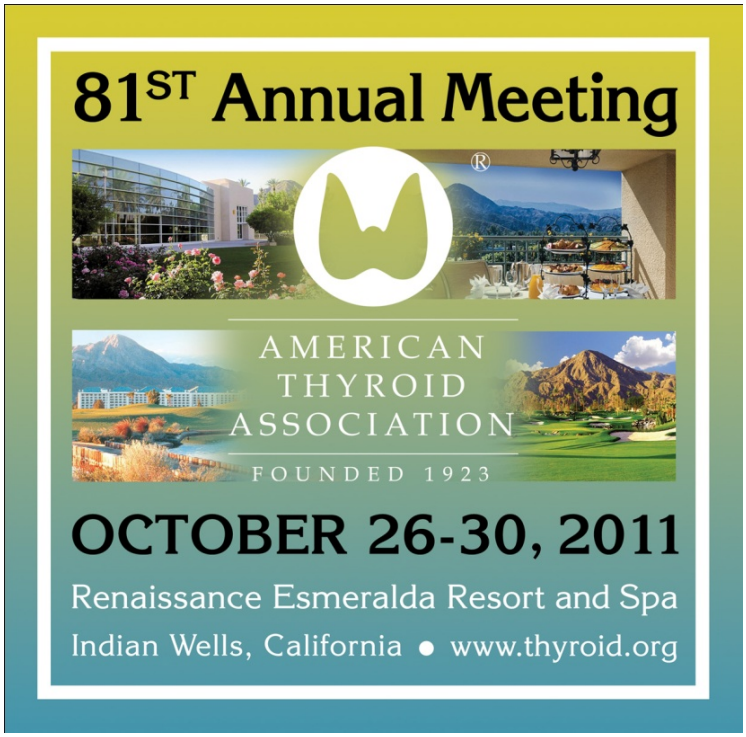

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Call for Nominations for 2011
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Board of Directors

In accordance with the Bylaws of the American Thyroid Association, the Nominating Committee is soliciting nominations from the membership for candidates for the offices of President and Directors (2) to serve on the ATA Board of Directors. Candidates will be selected by the Nominating Committee and submitted to the ATA Board in June 2011.

A ballot will be sent to the membership electronically in late August 2011. Newly elected Board members will be announced at the Annual Business Meeting on Thursday, October 27, 2011.

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Nominee: _____

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Two **Directors** will each serve a four-year term (2011-2015). See job description in Policies and Procedures under "Members Only" at www.thyroid.org. *Election of directors will be competitive.*

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All nominations must be submitted to the Executive Director, Bobbi Smith, by letter, fax, or e-mail bsmith@thyroid.org by April 30, 2011.

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