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Clinical Thyroidology

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An Invitation to Readers of *Clinical Thyroidology*

I would like to invite readers of *Clinical Thyroidology* who are not members to join the American Thyroid Association (ATA).

Founded nearly 80 years ago (1923), the ATA is the leading professional organization focused on the thyroid gland. The ATA's primary missions are to promote scientific and public understanding of the biology of the thyroid gland and its disorders and to improve methods for the prevention, diagnosis, and treatment of patients with thyroid disorders.

The goals of the ATA include:

- Fostering and supporting research on the biology, physiology, and disorders of the thyroid.
- Disseminating new knowledge that leads to prevention, diagnosis, and treatment of thyroid disorders.
- Supporting education concerning the investigation, diagnosis, and treatment of thyroid disorders.
- Establishing and promoting policies on the causes, diagnosis, and treatment of thyroid disorders.

The ATA offers its members many educational activities. We publish two journals—*Clinical Thyroidology* and *Thyroid*; hold annual scientific and clinical meetings; and sponsor seminars and courses. The ATA's flagship annual meeting, which this year will be held in Los Angeles from October 9 to 13, brings together approximately 1000 physicians and investigators from around the world to share the newest basic and clinical thyroid research. We also develop and publish guidelines for the diagnosis and treatment of thyroid disorders, develop patient information materials, and guide public policy on thyroid-related issues. Members are encouraged to participate in all these activities.

Information about the educational and other activities of the ATA, including information about membership, the prerequisites for membership, and an application form, can be found on our website, www.thyroid.org.

The ATA speaks for the community of thyroidologists and their patients. I hope those of you who are not ATA members will consider joining. I am confident you will find membership informative and rewarding.

Carole A. Spencer, Ph.D., F.A.C.B.
President

Clinical Thyroidology is now available
on the ATA web site (www.thyroid.org).

Atrial fibrillation is as common in patients with subclinical hyperthyroidism as in those with overt hyperthyroidism

Auer J, Scheibner P, Mische T, Langsteiger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. *Am Heart J* 2001;142:838-42.

SUMMARY

Background Atrial fibrillation is a well-known manifestation of overt hyperthyroidism, and subclinical hyperthyroidism may be a risk factor for atrial fibrillation. Among patients with idiopathic atrial fibrillation, the frequency of overt or subclinical hyperthyroidism has varied considerably, ranging from 0 percent to as high as 15 percent in different studies. This study was undertaken to determine the frequency of atrial fibrillation in patients with overt or subclinical hyperthyroidism and euthyroid patients evaluated at the same institution.

Methods The study subjects were 1338 consecutive patients with hyperthyroidism, of whom 725 had overt hyperthyroidism (low serum thyrotropin [TSH] concentrations and high serum free thyroxine [T₄] and free triiodothyronine [T₃] concentrations) and 613 had subclinical hyperthyroidism (low serum TSH concentrations alone), and 22,300 patients who had normal serum TSH concentrations. The time intervals were 1986 to 1995 for the patients with hyperthyroidism and 1989 to 1994 for the euthyroid patients. Whether the patients were inpatients or outpatients is not stated. All the patients were ≥45 years old; the reasons for testing included screening and suspected thyroid disease. Patients taking thyroid hormone were excluded. Among the patients with hyperthyroidism, 85 percent had a multinodular goiter and 15 percent had Graves' disease.

Atrial fibrillation was diagnosed by electrocardiography. In patients with atrial fibrillation, other risk factors for atrial fibrillation were sought, echocardiography was performed, and treatment records were reviewed.

Results The frequency of atrial fibrillation was 2.3 percent in the euthyroid patients, 13.8 percent in those with overt hyperthyroidism, and 12.7 percent in those with subclinical

hyperthyroidism (Table 1). As compared with the euthyroid group, the relative risk of atrial fibrillation in the overt hyperthyroidism group was 5.8 (95 percent confidence interval, 2.7 to 8.5; P<0.01) and the relative risk in the subclinical hyperthyroidism group was 5.2 (95 percent confidence interval 2.1 to 8.7; P<0.01).

	No. at Risk	Age (yr)*	No. with Atrial Fibrillation (%)
Euthyroid	22,300	66±8	513 (2.3)
Overt hyperthyroidism	725	67±8	100 (13.8)
Subclinical hyperthyroidism	613	68±9	78 (12.7)

*Mean±SD.

Among the patients with atrial fibrillation, there were no differences in frequency of coexisting cardiovascular disease (Table 2)

	No.	Hypertension	Left Ventricular Hypertrophy	Cardiac Disease*
Euthyroid	513	25%	29%	61%
Overt hyperthyroidism	100	29%	24%	65%
Subclinical hyperthyroidism	78	13%	29%	57%

*Coronary artery disease, dilated cardiomyopathy, or valvular heart disease.

After antithyroid treatment, 24 of the 100 patients (24 percent) with overt hyperthyroidism and 15 of the 78 patients (19 percent) with subclinical hyperthyroidism converted to sinus rhythm (time intervals not stated). The rate of conversion was higher in patients who had no cardiovascular disease; for example, among the patients with subclinical hyperthyroidism, 36 percent of those who converted had cardiovascular disease, as compared with 77 percent of those who did not have cardiovascular disease.

Conclusion The frequency of atrial fibrillation is increased to a similar degree in patients with overt hyperthyroidism and in those with subclinical hyperthyroidism.

COMMENTARY

That atrial fibrillation was more common in patients with overt hyperthyroidism than in euthyroid patients in this study is not surprising. What is surprising is that it was as common in the patients with subclinical hyperthyroidism as in those with overt hyperthyroidism. The diagnosis of overt hyperthyroidism was based on standard criteria, and all the patients had serum TSH concentrations ≤0.03 mU/L (normal, 0.4 to 4.0; assay sensitivity, <0.01).

The diagnosis of subclinical hyperthyroidism was also based on standard criteria—low serum TSH and normal serum free T₄ and T₃ concentrations—but some patients with nonthyroidal illness have similar findings. Also, the measurements may have been done only once, and no doubt many of the patients had only a slightly low serum TSH concentration. Therefore, some of the 613 patients with subclinical hyperthyroidism may have had low serum TSH concentrations as a result of nonthyroidal illness, not subclinical hyperthyroidism.

No one questions the need to look for hyperthyroidism in patients with atrial fibrillation, or the need to treat it if found. The latter surely applies to subclinical hyperthyroidism as well as overt hyperthyroidism, but before antithyroid therapy is initiated care must be taken to ensure that the patient's low serum TSH concentration is a result of thyroid hyperfunction and not nonthyroidal illness.

Robert D. Utiger, M.D.

Recurrence of ventricular tachyarrhythmias in patients with amiodarone-induced hyperthyroidism

Shiga T, Wakaumi M, Matsuda N, Shoda M, Hagiwara N, Sato K, Kasanuki H. Amiodarone-induced thyroid dysfunction and ventricular tachyarrhythmias during long-term therapy in Japan. *Jpn Circ J* 2001;65:958-60.

SUMMARY

Background Amiodarone is an accepted therapy for patients with a ventricular tachyarrhythmia, but it has important side effects. They include both hyperthyroidism and hypothyroidism. The former in particular might be expected to result in recurrence of an arrhythmia. This study was undertaken to determine the frequency of recurrences of ventricular tachyarrhythmias in patients who were treated with amiodarone and then had hyperthyroidism or hypothyroidism while taking the drug.

Methods The study subjects were 232 consecutive patients with ventricular tachycardia or fibrillation and organic heart disease who were treated with amiodarone. Serum free thyroxine (T_4), free triiodothyronine (T_3), and thyrotropin (TSH) were measured and Holter monitoring was done every three months for two years or until death or cessation of amiodarone therapy in all patients. Plasma amiodarone and desethylamiodarone, the active form of the drug, were measured in some patients.

Hyperthyroidism was defined as a serum TSH concentration $<0.1 \mu\text{U/mL}$ (normal range, 0.2 to 4.0) and a high normal or high serum free T_4 or free T_3 concentration. Hypothyroidism was defined as a serum TSH concentration $\geq 10 \mu\text{U/mL}$ and a low serum free T_4 concentration. Recurrent sustained ventricular arrhythmias, with or without symptoms, were diagnosed by electrocardiography, Holter monitoring, or recording from an implantable defibrillator.

Results During follow-up 179 patients (77 percent) remained euthyroid, 29 (12 percent) had hyperthyroidism, and 25 (11 percent) had hypothyroidism (1 patient had both). At base line, the mean age of the patients in the euthyroid, hyperthyroid, and hypothyroid groups was similar (53, 51, and 54 years, respectively), as were the proportions of women and men, types of cardiac disease, mean

values for left ventricular ejection fraction, and type of ventricular tachyarrhythmia (tachycardia or fibrillation). The tachyarrhythmia was controlled by amiodarone in most patients (number not stated) before the onset of thyroid dysfunction. Hyperthyroidism was diagnosed 32 ± 12 (mean \pm SD) months and hypothyroidism 18 ± 14 months after the initiation of amiodarone therapy.

Among the 29 patients who had hyperthyroidism, the mean heart rate and number of ventricular premature contractions per 24 hours were significantly higher when they were hyperthyroid than when they were euthyroid (heart rate, 71 ± 12 vs. 65 ± 8 beats/minute; premature ventricular beats, $2730 \pm 14,355$ vs. 806 ± 1736 per 24 hours). Nine of the 29 patients (31 percent) had recurrence of sustained ventricular tachycardia when hyperthyroid and 1 (3 percent) when euthyroid. In contrast, among the 25 patients who had hypothyroidism, the mean heart rate and number of ventricular premature contractions per 24 hours were similar when they were hypothyroid and when they were euthyroid; 1 patient (4 percent) each had sustained ventricular tachycardia when hypothyroid and when euthyroid. No patient in either group had ventricular fibrillation or died suddenly. The doses of amiodarone and the plasma concentrations of amiodarone and desethylamiodarone were similar in the patients who had hyperthyroidism and those who had hypothyroidism, and did not differ when the patients were euthyroid and when they had thyroid dysfunction. Whether any of the patients who remained euthyroid during the 2-year follow-up period had a recurrent ventricular tachyarrhythmia is not stated.

Conclusion Patients with ventricular tachyarrhythmias who are treated with amiodarone are more likely to have recurrence of ventricular tachycardia if they have hyperthyroidism than if they remain euthyroid.

COMMENTARY

Ventricular tachyarrhythmias are rare in patients with hyperthyroidism. However, these patients with hyperthyroidism were unusual, because they had cardiac disease and a ventricular tachyarrhythmia before they had hyperthyroidism. Given that hyperthyroidism increases cardiac work and, according to this study, the frequency of ventricular premature contractions in patients with a history of ventricular tachyarrhythmias, it does not seem surprising that hyperthyroidism

might be associated with recurrent ventricular tachycardia, despite the antiarrhythmic actions of amiodarone and the ability of amiodarone and desethylamiodarone to block adrenergic pathways and binding of T_3 to its receptors.

There is no mention of whether the ventricular tachycardia subsided when the hyperthyroidism subsided, which it did either spontaneously or in response to methimazole or prednisone therapy; amiodarone was discontinued in only three of the patients. There also is no mention of atrial tachyarrhythmias,

despite their well-known association with hyperthyroidism. Indeed, the onset of new or recurrent atrial tachyarrhythmias is often the first manifestation of hyperthyroidism in patients treated with amiodarone, because of the patients' vulnerability to arrhythmias and the reduced expression of the typical manifestations of hyperthyroidism in patients with chronic cardiac disease.

Robert D. Utiger, M.D.

Lithium therapy can cause silent thyroiditis and hyperthyroidism

Miller KK, Daniels GH. Association between lithium use and thyrotoxicosis caused by silent thyroiditis. *Clin Endocrinol* 2001;55:501-8.

SUMMARY

Background Lithium carbonate is well known to have antithyroid actions, and hypothyroidism and goiter are among the most common side effects of lithium therapy. Lithium therapy also has been associated with hyperthyroidism caused by silent or painless (subacute lymphocytic) thyroiditis and hyperthyroidism caused by Graves' disease. This study examined the relationship between lithium therapy and hyperthyroidism caused by these two disorders.

Methods The study subjects were 100 consecutive patients with hyperthyroidism caused by silent thyroiditis and 300 consecutive patients with hyperthyroidism caused by Graves' disease. Hyperthyroidism caused by silent thyroiditis was defined as clinical and biochemical hyperthyroidism that spontaneously resolved, no thyroid tenderness, and a 24-hour thyroid iodine-123 (I-123) uptake of <10 percent. Hyperthyroidism caused by Graves' disease was defined as clinical and biochemical hyperthyroidism, a 24-hour thyroid I-123 uptake of >20 percent, and a diffuse pattern of I-123 uptake on a thyroid scan. Patients with normal or high serum thyrotropin concentrations and patients who had received iodine-containing radiographic contrast agents in the preceding 2 months were excluded. The hospital records were then searched to determine how many of the patients had measurements of serum lithium. The number of patients receiving lithium at the same hospital was estimated to allow calculation of the frequency of both causes of hyperthyroidism among patients taking lithium.

Results Among the 100 patients with hyperthyroidism caused by silent thyroiditis, 4 (4 percent) were taking lithium at the time of diagnosis and 2 (2 percent) had taken it within the preceding 6 months. Among the 300 patients with Graves' hyperthyroidism, 4 (1 percent) were taking lithium and none had taken it within the preceding 6 months. Among patients taking lithium the odds of hyperthyroidism caused by silent thyroiditis were 4.7 (95 percent confidence interval, 1.3 to 17.1), as compared with hyperthyroidism

caused by Graves' disease. The incidence of lithium-associated silent thyroiditis and hyperthyroidism was approximately 1.3 cases per 1000 person-years, and the incidence of lithium-associated hyperthyroidism caused by Graves' disease was 1.4 cases per 1000 person-years. The combined rate of 2.7 cases per 1000 person-years is higher than the estimated rate of hyperthyroidism of all causes (0.3 to 1.2 cases per 1000 person-years) in the general population.

Nine additional patients with lithium-associated hyperthyroidism (7 with silent thyroiditis, 1 with Graves' hyperthyroidism, and 1 with toxic multinodular goiter) were identified by review of records at the same hospital. The 13 patients with lithium-associated silent thyroiditis and hyperthyroidism included 8 women and 5 men; their mean (\pm SD) age was 34 ± 6 years. None of the women had been pregnant during the preceding year. Thyroid size was normal in 5 patients, and no more than 2 times normal size in the others. Thyroid 24-hour I-123 uptake values ranged from 0 to 5 percent. Serum antithyroid antibody concentrations were normal in 3 of the 6 patients in whom they were measured. The hyperthyroidism subsided spontaneously in the 12 patients for whom follow-up data were available (4 patients had hypothyroidism). The 5 patients with Graves' hyperthyroidism were all women. All had a goiter and high 24-hour thyroid I-123 uptake values, and in general they had higher serum thyroxine and triiodothyronine concentrations and lower serum thyrotropin concentrations than the patients with lithium-associated silent thyroiditis and hyperthyroidism. Most patients in both groups taking lithium had therapeutic serum lithium concentrations, but the duration of lithium therapy is not given.

Conclusion Hyperthyroidism caused by silent thyroiditis is associated with lithium therapy more often than is hyperthyroidism caused by Graves' disease, but both are more common in lithium-treated patients than in the general population.

COMMENTARY

How can lithium therapy be associated with both hypothyroidism and, less often, hyperthyroidism, especially since lithium has an antithyroid action not only in normal subjects but also in patients with hyperthyroidism caused by Graves' disease. The explanation is probably that lithium causes thyroid dysfunction in patients who have autoimmune thyroid disease, and it causes autoimmune thyroid disease (and thyroid dysfunction) in patients who are susceptible to it.

Lithium-associated hyperthyroidism seems to be a result of the ability of lithium to induce either silent thyroiditis or Graves' disease. In this study silent thyroiditis accounted for most cases. In another study of 14 patients with lithium-associated hyperthyroidism, 8 had Graves' disease, 2 had silent thyroiditis, 3 had a nodular goiter, and in 1 the cause was undetermined; the duration of lithium therapy in these 13 patients ranged from 1 to 11 years (1). In that study lithium therapy also was associated with an increased incidence of hyperthy-

roidism. The difference in the relative frequency of silent thyroiditis and Graves' disease as a cause of hyperthyroidism is unexplained.

Robert D. Utiger, M.D.

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No overall increase in major malformations, but possible increase in esophageal or choanal atresia, in infants of mothers treated with methimazole during pregnancy

Di Gianantonio E, Schaefer C, Mastroiacovo PP, Cournot MP, Benedicenti F, Reuvers M, Occupati B, Robert E, Bellemin B, Addis A, Arnon J, Clementi M. Adverse effects of prenatal methimazole exposure. *Teratology* 2001; 64:262-6.

SUMMARY

Background Congenital malformations are rare in infants of mothers who received an antithyroid drug during the first months of their pregnancies, but may be more common in infants of mothers who received methimazole than in infants of mothers who received propylthiouracil. Among the defects reported in these infants, aplasia cutis has received the most attention, but recent studies have linked methimazole to an embryopathy characterized by minor facial dysmorphic features, esophageal atresia with tracheoesophageal fistula, choanal atresia, anomalous development of nipples, and developmental delay. This prospective cohort study was undertaken to assess the risk of these and other anomalies in infants of women taking methimazole who were referred to a Teratology Information Service.

Methods The patient group consisted of 288 pregnant women with hyperthyroidism taking methimazole in a dose of 5 to 50 mg daily during the preconception period or the first trimester of pregnancy who were referred to 1 of 10 units of the European Network of Teratology Information Services for risk assessment. The control group consisted of 1089 pregnant women who were using drugs known not to be teratogenic (ampicillin, penicillin, skin creams not containing vitamin A, eye and nose drops) or who had diagnostic skull or limb x-rays while pregnant. At the time of the initial inquiry, information was sought from all the women about their current pregnancy and treatment and their medical and obstetrical history. Three to 12 months after the expected date of delivery, the women, their physicians, or both, were contacted by mail or telephone seeking information about the outcome of the pregnancy, type of delivery, infant characteristics, perinatal complications, and presence and type of major malformations. The latter were defined as structural anomalies having medical, surgical, or cosmetic importance. The interviewer did not know whether the woman was in the patient group or the control group.

Results Information about the outcome of pregnancy was obtained from 241 of the 288 women (84 percent) with hyperthyroidism who had taken methimazole; 47 women (16 percent) were lost to follow-up. Among these 241 women, the pregnancy was terminated spontaneously or electively in 39, and 200 delivered 202 live infants and 2 delivered stillborn infants. Among the 1089 control women, the pregnancy was terminated in 96 women, and 993 delivered 1002 live or stillborn infants (data provided by the authors). The frequency of spontaneous abortions in the two groups was 6 percent and 7 percent, respectively. The mean age of the mothers, gestational age at delivery, and birth weight and head circumference of the infants in the two groups were similar.

Among the 204 infants exposed to methimazole, 8 (4 percent) had one or more major malformations: 1 each had esophageal atresia, choanal atresia, craniosynostosis and hypospadias, scrotal hypospadias, scrotal hypospadias and hemivertebra, spinal bifida, ventricular septal defect, and atrioventricular canal. The mothers of these infants had taken methimazole (carbimazole in 2 mothers) for varying intervals, ranging from 4 to 7 weeks of gestation in the mother whose infant had choanal atresia to from before pregnancy to 37 weeks in the mother whose infant had an atrioventricular canal. Among the 1002 infants in the control group, 23 (2 percent, $P = 0.19$) had major malformations: 8 cardiac, 6 renal, 3 skeletal, 2 hypospadias, 1 diaphragmatic hernia, 1 ocular, 1 cystic hygroma, and 1 choroid plexus cyst.

Conclusion The frequency of major malformations is not higher in infants of mothers with hyperthyroidism who took methimazole before or early in pregnancy, as compared with infants whose mothers took nonteratogenic drugs, but the risk of esophageal or choanal atresia may be higher.

COMMENTARY

What has been called methimazole embryopathy, as defined above, has now been described in about 10 infants. Given this small number, the variations in manifestations, and the lack of information about dysmorphism and developmental delay in some of the reports, including this one, it may be premature to say that there is a methimazole embryopathy. Whether or not there is an embryopathy,

the linking of esophageal atresia or choanal atresia alone to methimazole in even a few cases is worrisome, given that these anomalies are said to occur in only 1 in 2500 and 1 in 10,000 infants, respectively. Aplasia cutis, another purported risk of methimazole exposure in utero, was not mentioned in this study, and presumably was not found.

However low the frequency of esophageal atresia, choanal atresia, and aplasia cutis may be in infants exposed to

methimazole in utero, these anomalies have not been described in infants of mothers treated with propylthiouracil. This difference may be real, but it could also reflect the facts that, worldwide, many more patients with hyperthyroidism are treated with methimazole (or carbimazole) than propylthiouracil, and that no one has studied propylthiouracil in the way these investigators studied methimazole.

Robert D. Utiger, M.D.

Thyrotropin-receptor antibodies may inhibit thyrotropin secretion

Brokken LJS, Scheenhardt JWC, Wiersinga WM, Prummel MF. Suppression of serum TSH by Graves' Ig: evidence for a functional pituitary TSH receptor. *J Clin Endocrinol Metab* 2001;86:4814-7.

SUMMARY

Background Patients who have hyperthyroidism have very low serum thyrotropin (TSH) concentrations, due to suppression of TSH secretion by the high serum concentrations of thyroxine (T₄) and triiodothyronine (T₃). When the patients are treated, and their serum T₄ and T₃ concentrations fall to normal or below, serum TSH concentrations rise to normal or above. In some patients the recovery of TSH secretion seems to be delayed beyond what would be expected, based on their serum T₄ and T₃ concentrations, suggesting that factors other than serum T₄ and T₃ inhibit TSH secretion. This study was undertaken to determine if TSH receptor-stimulating antibodies inhibit TSH secretion.

Methods The effect of TSH receptor-stimulating antibodies on TSH secretion was studied in rats. The rats were fed methimazole for one week, which resulted in mild hypothyroidism; they were then given one of three different preparations of IgG in a dose of 1 ml (30 mg) intravenously. Blood samples were collected for measurement of plasma TSH, T₄, and T₃ before and 1, 2, 4, 8, 24, and 48 hours after the injections.

The IgG was purified from serum by affinity chromatography and ammonium sulfate precipitation. One IgG preparation was purified from the serum of a normal subject (control IgG), one was purified from a pool of serum samples from 32 patients with hyperthyroidism caused by Graves' disease (high TSH receptor-stimulating IgG activity), and one was a mixture of the other two, prepared so that the TSH receptor-stimulating activity of the IgG mixture was 21 percent of that of the high TSH receptor-stimulating pool (intermediate TSH receptor-stimulating IgG activity).

The TSH receptor-stimulating antibody activity of the original serum samples is not given, but the activity of the IgG preparations, as determined by the ability of the IgG to inhibit the binding of TSH to thyroid membranes, was <5 U/L for the control IgG, 591 U/L for the IgG with high TSH receptor-stimulating activity, and 127 U/L for the IgG with intermediate TSH receptor-stimulating activity. The IgG preparations would not be expected to contain any TSH, and if it were present, it should not be detected in the immunoassay used to measure rat TSH.

Results The base-line plasma TSH, T₄, and T₃ concentrations in the three groups of rats (8 rats per group) were similar. After the injections of IgG, the 48-hour mean plasma TSH concentration in the rats that received the high-activity IgG preparation was 11 ng/mL, the value in the rats that received the intermediate-activity IgG preparation was 13 ng/mL, and the value in the rats that received the control IgG preparation was 16 ng/mL (values extrapolated from Figure 2 of the paper) (P<0.01). In all three groups, the mean base-line plasma TSH concentrations were approximately 10 ng/mL, and the plasma TSH concentrations were highest 2 hours after IgG injection. The peak plasma TSH concentrations were approximately 17 ng/mL in the rats that received the high-activity IgG preparation, 19 ng/mL in the rats that received the intermediate-activity IgG preparation, and 27 ng/mL in the rats that received the control IgG preparation (values extrapolated from Figure 1 of the paper).

Conclusion In patients with hyperthyroidism caused by Graves' disease, TSH secretion may be inhibited not only by the high serum T₄ and T₃ concentrations, but also by TSH receptor-stimulating antibodies.

COMMENTARY

The observation that formed the basis for the hypothesis that TSH receptor-stimulating antibodies might inhibit TSH secretion is that TSH secretion recovers slowly after thyroid secretion is reduced in patients with hyperthyroidism. In practical terms this means that measurements of serum TSH do not provide useful information in the first months after the initiation of antithyroid drug therapy or administration of radioiodine. The slow recovery is exemplified by a study in which serum TSH and free T₄ were measured at 2- to 4-week intervals for 6 months after radioiodine therapy in 21 patients with Graves' hyperthyroidism (1). Among these patients, 19 (90 percent) had low serum free T₄ concentrations and low or normal serum TSH

concentrations 63 days (mean; range, 27 to 119) after treatment, which persisted for 25 days (range, 14 to 47).

If TSH receptor-stimulating antibodies inhibit TSH secretion directly, they presumably do so by activating TSH receptors. The thyrotroph cells of the pituitary do not have TSH receptors, but the receptors are present on folliculostellate cells of the pituitary (2). Brokken et al. hypothesize that the antibodies activate the TSH receptors on these cells, which then secrete some factor(s) that acts to inhibit TSH secretion in a paracrine manner. If this pathway exists, TSH itself should also activate it. Thus, TSH would inhibit its own secretion, therefore reducing the ability of TSH to maintain thyroid secretion in patients with, for example, autoimmune thyroid disease. This is a reason to be skeptical

that TSH receptor-stimulating antibodies should be added to the list of factors that inhibit TSH secretion.

Robert D. Utiger, M.D.

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Serum from cats with hyperthyroidism does not activate feline thyrotropin receptors

Nguyen LQ, Arseven OK, Gerber H, Stein BS, Jameson JL, Kopp P. Cloning of the cat TSH receptor and evidence against an autoimmune etiology of feline hyperthyroidism. *Endocrinology* 2002;143:395-402.

SUMMARY

Background Hyperthyroidism is far more common in cats than in other animals. The usual causes are a toxic uninodular or multinodular goiter, but a few cats seem to have a diffuse goiter, raising the possibility that they have the feline counterpart of Graves' disease. This study was done to clone the feline thyrotropin (TSH) receptor, determine its structure, and define the properties of the receptor, including whether it can be activated by serum or serum immunoglobulins from cats with hyperthyroidism or humans with hyperthyroidism caused by Graves' disease. In addition, the effect of serum from cats and humans with hyperthyroidism was compared in a radioreceptor assay using porcine TSH receptors.

Methods RNA was isolated from feline thyroid tissue. Presumably the tissue was normal, but this is not stated. The RNA was reverse transcribed into two overlapping fragments of DNA using primers specific for the human TSH receptor. The resulting cDNA fragments were cloned and their sequence determined, after which the full-length receptor was generated. Its sequence then was determined and compared with that of the TSH receptor in other animals and humans.

Feline and human TSH receptor cDNA was transfected into human embryonic kidney cells (TSA-201) cells. TSH binding to the transfected receptors in these cells was measured by incubation of the cells with iodine-125 (I-125)-labeled bovine TSH and increasing amounts of unlabeled bovine TSH. The ability of serum or immunoglobulin G (IgG) fractions of serum from cats with hyperthyroidism and humans with hyperthyroidism caused by Graves' disease to stimulate cyclic AMP by the cells was determined. Lastly, the ability of serum from cats with hyperthyroidism

and humans with Graves' hyperthyroidism to inhibit the binding of labeled bovine TSH to solubilized porcine TSH receptors was determined.

The serum samples were obtained from 16 cats with hyperthyroidism and 3 patients with Graves' hyperthyroidism. The characteristics of the cats, including the results of pathological studies of thyroid tissue, are not described.

Results The feline TSH receptor was found to contain 763 amino acids, 1 amino acid less than the human, bovine, canine, murine, ovine, and rat TSH receptors. It most closely resembles the canine receptor (96 percent identity) and is 90 percent identical to the human TSH receptor. The functional characteristics of the transfected feline TSH receptors were similar to those of the transfected human TSH receptors. The TSH-binding affinity and capacity of cells transfected with feline and human TSH receptors were similar. Both types of cells produced some cyclic AMP in the absence of TSH, and the cyclic AMP responses to bovine TSH were much the same.

Serum and IgG fractions of serum from the 16 cats with hyperthyroidism did not stimulate cyclic AMP production in cells transfected with feline TSH receptors, whereas serum and IgG fractions from patients with Graves' hyperthyroidism did stimulate cyclic AMP production by these cells. Serum from cats with hyperthyroidism also did not inhibit the binding of I-125-labeled bovine TSH to solubilized porcine TSH receptors, whereas serum from patients with Graves' hyperthyroidism did inhibit binding.

Conclusion The structure of the feline TSH receptor is similar to that of the human TSH receptor. Serum from humans with Graves' hyperthyroidism, but not serum from cats with hyperthyroidism, activates feline TSH receptors.

COMMENTARY

Why hyperthyroidism should be much more common in cats than in other animals is not known, but it is not because there is a feline counterpart of Graves' disease. This absence is not because feline TSH receptors are somehow insensitive to TSH receptor-stimulating antibodies, because human TSH receptor-stimulating antibodies can activate the receptors. Instead, it is because cats with hyperthyroidism do not produce the antibodies. Indeed, TSH receptor-stimulating antibodies have never been detected in any animal species, notwithstanding the similar structures of TSH receptors

among species.

In cats, hyperthyroidism is usually caused by a thyroid adenoma or a multinodular goiter. For example, in a study of 131 cats with hyperthyroidism, 38 (29 percent) had a thyroid adenoma and 93 (71 percent) had a multinodular goiter (1). Why cats should be prone to formation of autonomously functioning thyroid nodules is a mystery. Risk factors seem to be the breed of cat (higher risk in Siamese and Himalayan than in other cats), use of litter, use of topical anti-parasitic compounds, and consumption of canned food (2).

Robert D. Utiger, M.D.

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Thyroxine treatment does not improve well-being or cognitive functioning in patients with symptoms of hypothyroidism who have normal thyroid function

Pollock MA, Sturrock A, Marshall K, Davidson KM, Kelly CJG, McMahan AD, McLaren EH. Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial. *BMJ* 2001;323:891-5.

SUMMARY

Background Symptoms such as fatigue, lethargy, weight gain, cold intolerance, and dry skin or hair are common not only in people with overt or subclinical hypothyroidism, but also in those who have normal thyroid function. In general, these symptoms improve during treatment with thyroxine (T_4) in people with hypothyroidism, but the effect of T_4 treatment in those with normal thyroid function has not been assessed in a controlled trial.

Methods Two groups of people were studied. One consisted of 25 patients (23 women and 2 men; mean [\pm SD] age, 48 ± 11 years) who had at least three of six symptoms that are common in patients with hypothyroidism for at least six months. These symptoms were lethargy, tiredness, weight gain or inability to lose weight, cold intolerance, hair loss, and dry hair or skin. The other group consisted of 19 normal subjects (17 women and 2 men; mean age, 49 ± 10 years) who had no symptoms. No study subject had any current medical illness or history of thyroid disease, and all had normal serum thyrotropin (TSH), free T_4 , and free triiodothyronine (T_3) concentrations.

The patients and normal subjects were given 0.1 mg of T_4 or placebo daily for 12 weeks, in random order and with a 6-week interval between treatment periods. Vital signs, psychological and physical well-being, cognitive functioning, and serum TSH, free T_4 , and free T_3 were measured before and at the end of each 12-week period. Psychological well-being was measured using the hospital anxiety and depression scale, and physical well-being and general health were measured using five scales of the Short Form-36 health survey. Cognitive functioning was measured using the logical memory, verbal paired associates, visual reproduction, and digit span tests from the Wechsler memory scale, and the trail-making test. Twenty-two of the patients and all 19 of

the normal subjects completed the study.

Results In both groups, serum free T_4 concentrations were higher and serum TSH concentrations were lower at the end of the T_4 -treatment period, as compared with the placebo period, and the magnitude of the changes was similar in both groups. For example, in the patient group the mean (\pm SD) serum TSH concentrations were 0.7 ± 0.8 mU/L after T_4 treatment and 1.8 ± 1.2 mU/L after placebo; the respective values in the group of normal subjects were 0.3 ± 0.4 and 1.6 ± 1.5 mU/L. Serum free T_3 concentrations were not different at the end of the two periods in the patient group but were higher at the end of the T_4 -treatment period than the placebo period in the group of normal subjects. There were no differences in pulse rate, blood pressure, or weight at the end of either period in either group.

At base-line, the patient group had higher levels of anxiety and depression, scored lower on the physical well being and general health scales of the Short Form-36 survey, scored lower on several tests of cognitive function, and had slower movements (trail-making test), as compared with the group of normal subjects.

In the patient group, there were small improvements in anxiety and depression, physical well-being, and general health during both the T_4 -treatment and placebo periods, with no difference between the two periods, but no changes in cognitive functioning during either period. There were no changes in any of the scores or tests during either period in the group of normal subjects.

Conclusion T_4 treatment does not improve psychological or physical well-being or cognitive functioning in patients who have some symptoms of hypothyroidism but normal thyroid function.

COMMENTARY

The patients in this study underwent many tests before and at the end of each treatment period, but it is curious that they were not asked whether the symptoms that made them eligible for the study improved during the treatment periods. These symptoms are not specific or sensitive indicators of the presence of hypothyroidism (1), but they are clues to its presence, and they would be expected to improve if they were due to some

very minor degree of thyroid deficiency not detected by measurements of serum TSH, free T_4 , and free T_3 . Along with their hypothyroid-like symptoms these patients had some other symptoms and disabilities at base line, as compared with the normal subjects, that improved to some minor extent during both the T_4 treatment and placebo periods and that cannot therefore be attributed to T_4 deficiency.

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Radiation therapy causes hypothyroidism in patients with head and neck cancer

Mercado G, Adelstein DJ, Saxton JP, Secic M, Larto MA, Lavertu P. Hypothyroidism: a frequent event after radiotherapy and after radiotherapy with chemotherapy for patients with head and neck carcinoma. *Cancer* 2001;92:2892-7.

SUMMARY

Background External-beam radiation therapy to the head and neck is well known to cause thyroid disease, especially hypothyroidism, in children and young adults. This therapy also causes hypothyroidism in older people with head and neck cancer. However, the overall risk of hypothyroidism and the contribution of patient or treatment factors to the risk have not been studied in much detail. In this study the frequency of hypothyroidism was determined in patients with head and neck cancer treated with radiation alone or radiation and chemotherapy.

Methods The study subjects were 143 patients with non-metastatic, resectable squamous-cell carcinoma of the head and neck (oral cavity, 6 patients; oropharynx, 68; larynx, 39; hypopharynx, 27; and unknown or multiple sites, 3). There were 110 men and 33 women, with a median age of 58 years (range, 24 to 77); 127 patients were white and 16 were black. Four patients had stage II tumors (tumor size >2 cm to ≤4 cm), 32 patients had stage III tumors (tumor size >4 cm, or tumor size ≤4 cm and metastasis to a single ipsilateral lymph node), and 103 had stage IV tumors (tumor of any size and invasion of local structures or metastases to one or more lymph nodes). Patients with thyroid dysfunction before treatment and those who underwent thyroid resection to control tumor were excluded.

Among the 143 patients, 89 were enrolled in a randomized trial of radiation therapy versus radiation therapy plus chemotherapy. The radiation dose was 6600 to 7200 cGy, given as single daily fractions of 180 to 200 cGy, and the

chemotherapy was 5-fluorouracil and cisplatin, both given as 4-day infusions twice during radiation therapy. The remaining 54 patients received the same radiation and chemotherapy regimen independent of the trial.

Serum thyrotropin (TSH) was measured before and at the end of treatment, and then at 3- to 6-month intervals. Hypothyroidism was defined as a serum TSH concentration >5.5 μU/mL.

Results The mean radiation dose to the site of the primary tumor was 6900 cGy (range, 4680 to 8020) and the mean dose to the neck was 5900 cGy (range, 4400 to 7680). The first cases of hypothyroidism were detected 4 months after the initiation of treatment. At 5 years, the incidence was 48 percent and at 8 years it was 67 percent, as estimated by Kaplan-Meier analysis. The median time to onset of hypothyroidism was 1.4 years (range, 0.3 to 7.2).

There was no relationship between patient age or sex, location of the primary tumor, tumor stage, or radiation dose to the primary site or the neck and the occurrence of hypothyroidism. Patients treated with radiation therapy alone and those treated with radiation plus chemotherapy were equally likely to develop hypothyroidism. At 5 years, none of the 16 black patients had hypothyroidism, as compared with a projected incidence of 52 percent among the 127 white patients (P = 0.02).

Conclusion Patients with squamous-cell carcinoma of the head and neck who are treated with high doses of radiation are at high risk for hypothyroidism.

COMMENTARY

The effect of external-beam radiation therapy on the thyroid gland in patients, usually older adults, with head and neck cancer seems to be limited to causing hypothyroidism. In contrast, in patients, usually children and young adults, with Hodgkin's disease, the same therapy causes not only hypothyroidism but also thyroid nodules, thyroid carcinomas, and Graves' disease (1).

With respect to hypothyroidism, radiation doses of 3000 cGy or more cause hypothyroidism in approximately 40 to 50 percent of patients of all ages by 10 years after treatment, and more cases occur thereafter (1). Although not noted by Mercado et al., the effect is dose-dependent.

In this and many other studies of

this topic the diagnosis of hypothyroidism was based on a single measurement of serum TSH or on information obtained from the patients. Often, no distinction was made between overt hypothyroidism, which everyone would treat, and subclinical hypothyroidism, which not everyone would treat. And the frequency of hypothyroidism, especially subclinical hypothyroidism, may have been overestimated; a patient given the diagnosis on the basis of a serum TSH value of, for example, 8.5 μU/mL, might well have had normal values later. Whatever the true frequency of hypothyroidism, it must be substantial, and therefore serum TSH should be measured periodically in all patients with any type of tumor who receive radiation therapy to the neck.

The simplest explanations for why

other thyroid disorders have not been found in patients with head and neck cancer treated with radiation are the relatively short duration of follow-up, usually 10 years at most, and the low frequency of the disorders. In the study of Sklar et al. (1), for example, few patients had either Graves' disease or a thyroid nodule less than 10 years after radiation therapy.

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Central hypothyroidism is a prominent feature of hypopituitarism

Regal M, Paramo C, Sierra JM, Garcia-Mayor RV. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. *Clin Endocrinol* 2001;55:735-40.

SUMMARY

Background The clinical manifestations, hormonal deficiencies, and causes of hypopituitarism are diverse, and little is known about its frequency in the general population. This study was undertaken to determine the frequency, causes, and extent of hormonal deficiencies in adults with hypopituitarism living in a defined region of Spain during two time periods.

Methods The number of patients aged 18 years and older with hypopituitarism in the registry of patients at the General Hospital of Vigo in northwestern Spain, was determined in 1992 and in 1999, and the number of new cases was determined during each intervening year. Most if not all patients with pituitary disease are referred to this hospital from the primary and secondary hospitals in the region. All the hospitals are part of the National Health Service of Spain, and 99 percent of the inhabitants of the region receive care at them. The mean numbers of adults in the population in 1992 and 1999 were 137,465 and 151,587, respectively; 52 percent were women and 48 percent were men at both times.

The diagnosis of hypopituitarism was based on the presence of a deficiency of one or more pituitary hormones at the time of initial evaluation, or six or more months after treatment in the patients with pituitary or peripituitary tumors. Pituitary hormone secretion was assessed as follows: basal serum growth hormone (GH) and insulin-like growth factor (IGF)-I; early-morning plasma corticotropin (ACTH) and serum cortisol; serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (in women) and testosterone (men); serum thyrotropin (TSH) and free thyroxine (T_4); serum prolactin; and urine volume and osmolality. Patients in whom the results were inconclusive underwent an insulin tolerance test (serum GH, plasma ACTH) and thyrotropin-releasing hormone (serum TSH, serum prolactin) and gonadotropin-releasing hormone (serum FSH, serum LH) stimulation tests. Standard cut-off values were used; for example, ACTH deficiency was diag-

nosed if the serum cortisol concentration after hypoglycemia was ≤ 20 $\mu\text{g/dL}$ (552 nmol/L).

Results In 1992, there were 40 patients with hypopituitarism in the registry (29 per 100,000 people) (table). In 1999, there were 69 patients (46 per 100,000 people), which included many of the patients identified in 1992. From 1993 to 1999, there were 4 to 9 new cases per year; the mean annual incidence rate was 4.2 per 100,000 people per year, and it did not change during that period.

Table. Characteristics of Patients with Hypopituitarism in Vigo, Spain, 1992 and 1999.

	1992	1999
No. of patients	40	69
Women/men	17/23	33/36
Age at diagnosis (mean \pm SD)	48 \pm 17	50 \pm 17
Causes		
Pituitary adenoma-secreting*	12 (30%)	22 (32%)
Pituitary adenoma-non-secreting	11 (28%)	20 (29%)
Non-pituitary tumor**	4 (10%)	6 (9%)
Idiopathic	7 (18%)	8 (12%)
Sheehan's syndrome	4 (10%)	4 (6%)
Other [†]	2 (5%)	9 (13%)

*Lactotroph adenoma: 6 in 1992, 9 in 1999; somatotroph adenoma: 5 in 1992, 9 in 1999; corticotroph adenoma: 1 in 1992, 4 in 1999.

**Craniopharyngioma, meningioma, ependymoma, chordoma.

[†]Eosinophilic granuloma, empty sella, Rathke's cleft cyst, cerebral aneurysm.

Among the 69 patients in 1999, the proportions with 1, 2, 3, 4, 5, and 6 hormonal deficiencies were, respectively, 21 percent, 15 percent, 23 percent, 19 percent, 15 percent, and 7 percent. The deficiencies were: FSH/LH, 87 percent; TSH, 64 percent; ACTH, 62 percent; GH, 61 percent; prolactin, 17 percent; and vasopressin, 20 percent. The frequency of deficiencies and the types of deficiency were similar in the patients with tumors and those with other disorders.

Conclusion In this region of Spain, the annual incidence of hypopituitarism remained constant for 7 years. The majority of patients had a pituitary or non-pituitary tumor, and TSH deficiency was as common as ACTH or GH deficiency.

COMMENTARY

The frequency of hormonal deficiencies, including TSH deficiency, among these patients was comparable to that of larger studies (1,2). With respect to TSH deficiency, the diagnosis was based primarily on measurements of serum TSH and free T_4 , presumably meaning a normal or low serum TSH concentration and a low serum free T_4 concentration. Thyrotropin-releasing hormone stimulation tests were done if the results of

these tests were not conclusive. This is not a good test for central hypothyroidism. Some patients with hypopituitarism who have normal serum TSH and free T_4 values have no serum TSH response to TRH, and others who have low or normal serum TSH and low serum free T_4 values have normal, but sometimes delayed, serum TSH responses to TRH. The proportions of patients in whom hypothyroidism—or other deficiencies—were diagnosed on the basis of basal hormone measurements or

provocative tests are not given.

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Severity of hypothyroidism and inadequate treatment limit school achievement in children with congenital hypothyroidism

Leger J, Larroque B, Norton J, on behalf of AFDPHE. Influence of severity of congenital hypothyroidism and adequacy of treatment on school achievement in young adolescents: a population-based cohort study. *Acta Paediatr* 2001;90:1249-56.

SUMMARY

Background Treatment of infants with congenital hypothyroidism in the first weeks of life prevents most of the neurodevelopmental defects that occur in infants treated later. However, some infants treated early have mild cognitive defects, especially those with severe hypothyroidism and those in whom treatment is suboptimal. In this study a large cohort of infants with congenital hypothyroidism treated soon after birth was evaluated in adolescence to determine more precisely those factors that might affect their achievement in school.

Methods From 1979 to 1985 5,192,614 newborn infants were screened for congenital hypothyroidism in France, of whom 1276 (1 in 4069, or 0.024 percent) were found to have persistent hypothyroidism, based on records maintained by the French Association for the Diagnosis and Prevention of Child Handicap (AFDPHE). Base-line clinical and laboratory data and hormonal values after treatment for 15 days were recorded. Follow-up information about treatment, school achievement (defined as entry into the sixth grade), and socioeconomic variables was obtained from the pediatricians caring for these children in 1994 and 1998. The final cohort consisted of 682 children who were <40 days old when treatment was started and whose age at entry into the sixth grade was known.

At diagnosis, symptoms and signs of hypothyroidism, such as inactivity, constipation, hypotonia, and umbilical hernia, were recorded; infants with three or more of these findings were considered to have symptomatic hypothyroidism. Many infants had measurements of bone age (distal femoral and proximal tibial epiphyses) and thyroid radionuclide imaging. The latter was classified as no thyroid tissue (athyreosis), ectopic thyroid tissue, or normally located thyroid tissue. Serum thyroxine (T₄) values at diagnosis were subdivided into those <4.1 or ≥4.1 µg/dL (53 nmol/L) (this was the mean value). Serum thyrotropin (TSH) was measured at most follow-up visits; the results were subdivided into three groups according to the frequency of high values.

Results The mean (±SD) age of the 682 children (493 girls, 189 boys) at the start of treatment was 23±7 days. The mean starting T₄ dose was 5.6±1.6 µg/kg/day. The proportion of children with hypothyroidism who entered the sixth grade at the usual time (September in the year of the child's

11th birthday) was similar to that of the national population. The respective values for late entry for girls and boys with hypothyroidism were 25 percent and 32 percent, as compared with 28 percent and 36 percent for normal girls and boys. Late entry also was related to parental socioeconomic status, having a single mother, and related factors. The effects of several base-line and treatment variables are shown in the table.

	% Of Children	Odds Ratio (95% CI)*
Entering Sixth Grade Late		
Ectopic or normal thyroid tissue vs. athyreosis	24% vs. 33%	1.6 (1.1-2.3)
Higher vs. lower serum T ₄ value at diagnosis	14% vs. 26%	2.2 (1.2-4.2)
Treatment started		
Age ≤15 days	33%	1.0
Age 16 to 25 days	25%	0.7 (0.4-1.2)
Age 26 to 40 days	27%	0.8 (0.4-1.3)
T ₄ dosage		
≥7 vs. <7 µg/kg/day	19% vs. 28%	1.8 (1.0-3.5)
Serum TSH values		
>20 vs. ≤20 mU/L after 15 days	10% vs. 25%	3.0 (1.2-7.3)
Serum TSH values ≥15 mU/L during treatment		
0 to 3 times	19%	1.0
4 to 10 times	35%	2.4 (1.4-4.0)
>10 times	42%	3.0 (1.4-6.6)

The numbers of children for whom data were available ranged from 202 to 682. *CI, confidence interval. For paired comparisons, the odds ratio shown is for the odds of a higher % in column 2. The odds ratios were adjusted for the child's sex and parental socioeconomic and other variables.

Factors associated with late entry into sixth grade were athyreosis, lower serum T₄ values at diagnosis, lower initial dose of T₄, inadequate treatment, and absence of both epiphyses; in a multivariate analysis inadequate treatment and parental socioeconomic status had the greatest impact on late entry. Factors not associated with late entry were age at start of treatment, and presence of symptoms and signs of hypothyroidism.

Conclusion Children with severe congenital hypothyroidism and those who receive inadequate treatment are at risk for poor school achievement.

Athyreosis and slow onset of adequate treatment are associated with learning and memory deficits in children with congenital hypothyroidism

Song S-I, Daneman D, Rovet J. The influence of etiology and treatment factors on intellectual outcome in congenital hypothyroidism. *J Dev Behav Pediatr* 2001;22:376-84.

SUMMARY

Background Early treatment of children with congenital hypothyroidism is very effective in preventing major developmental delay, but school achievement may nonetheless be delayed, as for example reported by Leger et al. on the opposite page. More detailed studies of these children have revealed that some have cognitive impairment, including limitations in attention, language, and memory. This study was done to determine the relationships between specific cognitive abilities and the severity and adequacy of treatment of children with congenital hypothyroidism.

Methods The study subjects were 65 children 7 to 12 years old (mean, 9 years; 37 girls and 25 boys) with congenital hypothyroidism detected by neonatal screening between 1986 and 1992. They were recruited from among all children of this age (number not stated) treated at the Hospital for Sick Children in Toronto, Canada. Among them, 18 had no detectable thyroid tissue (athyreosis), 27 had ectopic thyroid tissue, and 17 had normally located thyroid tissue. The mean (\pm SD) age at which thyroxine (T_4) treatment was initiated was 17 ± 29 days; the initial dose of T_4 was 9 ± 2 μ g/kg/day. The children were evaluated regularly for 3 years.

The tests done for the study included the Vocabulary, Arithmetic, Coding, and Symbol Search subtests of the Wechsler Intelligence Scale for Children, the Attention/Executive, Language, Visuospatial, and Sensorimotor domains of a neuropsychological test for children, and the Children's Memory Scale.

Results The clinical characteristics, serum thyrotropin (TSH) concentrations, and initial T_4 doses were similar in the children with athyreosis, ectopic thyroid tissue, and normally located thyroid tissue, but the children with athyreosis

had lower serum T_4 concentrations. The children in the athyreosis group were less likely to have normal serum TSH concentrations during the first three months of treatment, and their dose of T_4 was adjusted more often during the first year of treatment, as compared with the other two groups.

The children in the athyreosis group scored lower on many components of the Wechsler Intelligence Scale for Children, whereas the scores for the other 2 groups were similar (table).

WISC tests*	Athyreosis	Ectopic Thyroid	Normal Thyroid
Full-scale IQ**	92 \pm 11	98 \pm 20	103 \pm 16
Verbal IQ	95 \pm 13	96 \pm 20	102 \pm 17
Performance IQ**	89 \pm 12	98 \pm 21	106 \pm 16
Vocabulary	9 \pm 3	9 \pm 5	10 \pm 3
Arithmetic**	8 \pm 2	8 \pm 4	11 \pm 4
Coding**	8 \pm 2	9 \pm 4	11 \pm 3
Symbol Search	10 \pm 2	11 \pm 5	12 \pm 3

*WISC, Wechsler Intelligence Scale for Children.
**P<0.05 for comparisons across all three groups.

The children in the athyreosis group also scored lower on some of the other tests. The scores on these tests and the Children's Memory Scale were lower in all children who had high serum TSH concentrations during the first three months of treatment, as compared with the children with normal concentrations at these times. Also, the scores on several tests were positively correlated with serum T_4 concentrations and negatively correlated with serum TSH concentrations at the time of testing.

Conclusion Children with congenital hypothyroidism caused by athyreosis and those in whom treatment does not lower TSH secretion to normal quickly are at increased risk for learning and memory deficits at age 6 to 12 years.

COMMENTARY

These two studies provide more evidence that the cause of congenital hypothyroidism is one determinant of outcome. Children with athyreosis are more likely to have clinical manifestations of hypothyroidism at birth, and lower serum T_4 concentrations at diagnosis.

The more important findings of these studies are those related to treatment. Leger et al. found that age at the start of treatment was not a determinant of school achievement, but that the initial T_4 dose was; these topics were not addressed by Song et al. Surely age does make a difference, but perhaps not in the

presence of other variables such as initial dose of T_4 , dose escalation, time to normalization of TSH secretion, and subsequent adequacy of treatment. With respect to initial dose of T_4 , there is general agreement that it should be in the range of 10 to 12 μ g/kg/day. Given the importance of a rapid fall in serum TSH concentrations, a finding in both studies, giving the more rapidly acting triiodothyronine together with T_4 for the first weeks of treatment bears consideration.

Assessment of school achievement as a delay in entering sixth grade is a rather crude test of cognitive function, because it means simply that the child had to repeat an earlier year of school.

In contrast, Song et al. did approximately 20 different tests, covering many aspects of attention, learning, and memory, with for the most part concordant results on similar types of tests. Their finding of correlations between some test results and serum T_4 or TSH concentrations (all within their respective normal ranges) at the time of testing suggests an immediate effect of T_4 , and at the same time tends to confuse the overall results. Nonetheless, the macroanalysis of Leger et al. and the microanalyses of Song et al. complement each other well.

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Recommendations for evaluation and treatment of patients with nontoxic multinodular goiter vary widely

Bonnema SJ, Bennedbaek FN, Ladenson PW, Hegedus L. Management of the nontoxic multinodular goiter: a North American survey. *J Clin Endocrinol Metab* 2002;87:112-7.

SUMMARY

Background Nontoxic multinodular goiter is among the most common thyroid disorders. Despite the frequency of these goiters, their clinical manifestations, consequences, and natural history, so far as these are known, are diverse. As a result, patients with these goiters are evaluated and treated in many different ways. In this study, thyroidologists in the United States were asked how they would evaluate and treat different patients with a multinodular goiter.

Methods A questionnaire describing patients with a multinodular goiter was sent to 270 clinically active members of the American Thyroid Association. Responses were received from 140 (52 percent). The results were compared with those of 120 clinically active members of the European Thyroid Association (approximately 65 percent of those queried).

The index case was a 42-year-old woman with a multinodular goiter estimated to weigh 50 to 80 g; the goiter had been present for 3 to 5 years. The patient had no symptoms of thyroid dysfunction, but did have "moderate local neck discomfort". There was no history of head or neck radiation and no family history of thyroid disease. Eleven variations of this patient were described, each varying by a single characteristic, for example, age, sex, size of goiter, rate of growth of the goiter, and serum thyrotropin (TSH) concentration. The clinicians were asked to choose from a list of diagnostic tests and treatments what they would do for the index patient and what they would do differently for the other patients.

Results For the index case, the serum tests ordered and percentages of respondents ordering that test were: TSH, 100 percent; free thyroxine (T₄), 54 percent; triiodothyronine (T₃), 23 percent; antithyroglobulin antibodies, 34 percent; antithyroid peroxidase or microsomal antibodies, 78 percent; and calcitonin, 4 percent. The *in vivo* diagnostic

tests and the percentages of respondents ordering them were: ultrasonography, 59 percent; scintigraphy, 24 percent; both ultrasonography and scintigraphy, 11 percent; and no imaging, 29 percent. Fine-needle aspiration biopsy would be done by 74 percent.

With respect to treatment of the index case, 56 percent of clinicians would recommend T₄ therapy, 36 percent periodic reevaluation, 1 percent radioiodine therapy, and 6 percent surgery. Among those recommending T₄ therapy, most (76 percent) would aim for a slightly low serum TSH concentration (0.1 to 0.3 mU/L).

Among the variations in the index case, a low serum TSH concentration had the largest effect on diagnosis and treatment: 58 percent of respondents would order radioiodine uptake and 61 percent scintigraphy; 56 percent would recommend radioiodine therapy; and none would recommend T₄ therapy. For a 75-year-old woman, 34 percent would still recommend T₄ therapy, and so would approximately 45 percent if the goiter in the index patient was small (30 to 50 g) and she had no neck discomfort. Variations that increased the likelihood that the patient might have a nodule that was a thyroid carcinoma led more often to biopsy and surgery as recommended therapy.

Virtually all tests were ordered more often by the European clinicians; for example, 32 percent would order measurements of serum calcitonin, and 69 percent both ultrasonography and scintigraphy. These clinicians would treat the index patient in the same way, but would recommend surgery more often for other patients.

Conclusion Thyroidologists in North America vary widely in their use of diagnostic tests and their recommendations for treatment in patients with a nontoxic multinodular goiter.

COMMENTARY

The most remarkable findings of this study were the high percentages of clinicians who recommended T₄ therapy for the index and other patients. This recommendation is probably based on the view that most patients want some treatment, and that T₄ therapy is simple and safe. However, few patients with a multinodular goiter have a decrease in goiter size, and just about any dose of T₄ can cause subclinical hyperthyroidism in them.

Studies of this type provide interest-

ing information about what clinicians may do, but the results should not be taken too seriously. The cases are created as typical cases, but of course there are no typical cases. The patient's personal perspective is lacking. What does the patient think about the problem, and what does she or he want done? Is the patient fearful of carcinoma, or unconcerned? What does "moderate local neck discomfort" mean? The answers to these questions should have an effect on what tests are done or what treatment, if any, is recommended. Moreover, clinicians do

not have to order all the tests at once, and indeed should not; rather, they should order a few tests, consider the results, and then make decisions about further testing. Other confounding problems are the low response rates to questionnaires of this type, and the question of whether the respondents actually do what they say they do. The only way to know is to audit records, and this has never been done for patients with thyroid disease.

Robert D. Utiger, M.D.

Seven percent of patients with thyroid nodules who have nondiagnostic biopsies have thyroid carcinoma

Chow LS, Gharib H, Goellner JR, van Heerden JA. Nondiagnostic thyroid fine-needle aspiration cytology: management dilemmas. *Thyroid* 2001;11:1147-51.

SUMMARY

Background In patients with thyroid nodules, cytologic examination of specimens obtained by fine-needle aspiration biopsy is the best test to distinguish between a thyroid carcinoma and a benign nodule. However, approximately 5 to 20 percent of biopsy specimens are reported as nondiagnostic, because the specimen may contain only a few cells, or the cells may be degenerating or otherwise unsuitable for analysis. This study was done to determine the outcome in patients who had a biopsy reported as nondiagnostic in a single year at a single institution.

Methods In 2000 the records were reviewed of all patients who had a fine-needle aspiration biopsy of a thyroid nodule reported as nondiagnostic at the Mayo Clinic in 1994. The biopsies were guided by palpation, and were considered nondiagnostic if the specimens contained fewer than six groups of 10 to 15 well-preserved thyroid follicular cells, or there was excessive drying or a large amount of blood. Further evaluation was at the discretion of the patient's physician. For the study, information was obtained about patient characteristics, findings on physical examination, results of laboratory studies, results of repeat biopsies, surgical and pathological findings, and follow-up to 2000 or the last visit to the clinic. Incidental thyroid carcinomas found at surgery were not recorded.

Results During 1994, 937 fine-needle aspiration biopsies of thyroid nodules were done, of which 182 (19 percent), done in 154 patients, were nondiagnostic. The study group consisted of 153 patients (1 patient declined) (109 women and 44 men; mean age, 52 years [range, 16 to 84]). Physical examination revealed a single nodule in 83 patients (54 per-

cent), multiple nodules in 33 patients (22 percent), a diffuse goiter in 18 patients (12 percent), and other findings in the remainder.

Another biopsy was done in 60 patients (39 percent); it was guided by palpation in 25 patients and by ultrasonography in 35 patients. Among these 60 patients, the cytology was considered benign in 30 (50 percent), suspicious in 5 (8 percent), malignant in 2 (3 percent), and nondiagnostic in 23 (38 percent), with little difference in results according to the type of biopsy. Ten of these 60 patients had surgery, which revealed carcinoma in 6. Of the 93 patients (61 percent) who did not have another biopsy, 17 had surgery, which revealed carcinoma in 4. Thus, 10 patients had a carcinoma, of which 6 were papillary carcinomas and 1 each was a Hurthle-cell carcinoma, anaplastic carcinoma, medullary carcinoma, and metastatic carcinoma. The 10 patients with a carcinoma constituted 7 percent of the entire group and 37 percent of the 27 patients who had surgery.

Among the 126 patients (82 percent) who did not have surgery, 73 (58 percent) had one nondiagnostic biopsy, 23 (18 percent) had two nondiagnostic biopsies, and 30 (24 percent) had a second biopsy that revealed benign cells. These 126 patients were followed for a mean (\pm SD) duration of 2.4 ± 2.3 years. Among the 52 patients followed for at least 1 year, 13 (25 percent) had resolution of thyroid disease (treatment, if any, not stated), 23 (44 percent) had stable thyroid disease, 5 (10 percent) died of unrelated disease, and the status of 11 (21 percent) was not known.

Conclusion In some patients with thyroid nodules in whom fine-needle aspiration biopsy is nondiagnostic the nodule is a thyroid carcinoma.

COMMENTARY

Biopsies of thyroid nodules that are nondiagnostic should be distinguished from those that are suspicious. Nondiagnostic really means inadequate, and it would be better to use that term. Suspicious biopsies are those that are technically adequate, but are in fact truly nondiagnostic. The cytopathologist cannot make a diagnosis of carcinoma, but on the other hand is not convinced the cells are benign.

If all patients who had a nondiagnostic biopsy were studied further, until the nodule was categorized as benign or malignant, how many would prove to have a carcinoma? In the study by Chow et al., 7 percent of the patients with a

nondiagnostic (inadequate) biopsy had a carcinoma, but this is a minimum estimate because many patients did not have a second biopsy or surgery. Among large groups of patients with thyroid nodules, about 5 to 10 percent of first biopsies reveal malignant cells, and nearly all are confirmed as carcinomas on pathological examination. Therefore, patients with thyroid nodules who have nondiagnostic biopsies are as likely to have a carcinoma than are patients with thyroid nodules in general. However, there are no studies in which all patients with nondiagnostic biopsies underwent surgery.

What can be done to reduce the frequency of nondiagnostic biopsies? One is to do the biopsy with ultrasound guidance. In several studies the frequency

of nondiagnostic ultrasound-guided biopsies was about half that of palpation-guided biopsies (1,2).

Robert D. Utiger, M.D.

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Thirty percent of patients with thyroid nodules given a cytologic diagnosis of follicular tumor have thyroid carcinoma

Baloch ZW, Fleischer S, LiVolsi VA, Gupta PK. Diagnosis of “follicular neoplasm”: a gray zone in thyroid fine-needle aspiration cytology. *Diagn Cytopathol* 2002;26:41-4.

SUMMARY

Background Among patients with thyroid nodules who undergo fine-needle aspiration biopsy, approximately 10 to 20 percent have biopsies designated follicular tumors or neoplasms. Most follicular tumors are benign, but some are carcinomas. Distinguishing among them requires excision of the nodule and examination of histologic sections looking for invasion of blood vessels and the capsule of the tumor by tumor cells. This study was done to determine what specific pathologic entities constitute follicular tumors and if the clinical characteristics of patients with follicular tumors differ according to the histologic diagnosis.

Methods and Results During the three-year period (January 1998 to December 2000), there were 167 patients with thyroid nodules in whom ultrasound-guided fine-needle aspiration biopsy of 184 nodules revealed follicular, including Hurthle-cell, tumors (17 patients had two nodules). The criteria for this diagnosis were: many cells of uniform appearance, scant colloid, and nuclear crowding and overlapping, but absence of the nuclear features of papillary carcinoma. These 184 nodules constituted 18 percent of the 1024 biopsies done during that interval. The nodules ranged in size from 1.0 to 6.0 cm, as determined by ultrasonography. The cytologic diagnosis was follicular tumor in 169

nodules and Hurthle-cell tumor in 15 nodules.

Among the 167 patients, 139 (83 percent) were women and 28 (17 percent) were men (age range, 23 to 80 years). Surgery was performed in 122 patients (73 percent)—thyroid lobectomy in 96 and thyroidectomy in 26. There were 85 benign nodules (70 percent) and 37 malignant nodules (30 percent). The histologic diagnoses are shown in the table.

Benign		Malignant	
Hyperplastic nodule	85 (60%)	Follicular variant of papillary carcinoma	25 (68%)
Follicular adenoma	17 (20%)	Follicular carcinoma	7 (19%)
Hurthle-cell adenoma	11 (13%)	Hurthle-cell carcinoma	4 (11%)
Lymphocytic thyroiditis	6 (7%)	Medullary carcinoma	1 (3%)

The nodule was a carcinoma more often among the men (47 percent) than the women (29 percent; $P < 0.01$), in patients ≥ 40 years old (20 percent) than those < 40 years old (10 percent, $P < 0.01$), and if the nodule was ≥ 3 cm (55 percent) than if it was < 3 cm (23 percent; $P < 0.01$).

Conclusion A substantial minority of thyroid nodules with cytologic characteristics of follicular tumors are thyroid carcinomas.

COMMENTARY

The proportion of follicular tumors that proved to be carcinomas was higher in this study than in some other studies, no doubt because all patients did not have surgery. For example, in a study of 120 patients with follicular tumors in which all the patients had surgery, 21 (18 percent) had carcinomas (1). Baloch et al. do not say why surgery was not done in all their patients, but the main reason must have been an assessment that the likelihood of thyroid carcinoma was small. This assessment was probably based on the characteristics of both the patients, such as age and sex, and the nodules, such as size and consistency. As demonstrated in this and other studies (1), however, none of these characteristics reliably distinguishes between benign and malignant nodules. Tests for several mutations and cellular proteins may do so, but none has yet gained general acceptance. One finding that does positively identify a follicular tumor as being benign is that it is hyperfunctioning on a

radionuclide scan. This test is appropriately done first in patients with thyroid nodules who have a low serum thyrotropin (TSH) concentration; if the nodule is hyperfunctioning a biopsy is not needed. The test should be considered before referral for surgery in patients with follicular tumors who have normal serum TSH concentrations, because some autonomously functioning thyroid adenomas do not make sufficient thyroid hormone to reduce TSH secretion to below normal.

Another reason for the high proportion of carcinomas in this study may be the classification of many tumors as follicular variant of papillary carcinoma. These carcinomas are characterized by cells that have the nuclear features of papillary carcinoma—crowded nuclei, ovoid nuclei, pale chromatin, nuclear grooves—and are arranged in micro- or macrofollicles. Most of these tumors are encapsulated, and blood vessel or capsular invasion is not seen. The nuclear changes may be multifocal, rather than seen uniformly throughout the tumor,

and the extent of the changes may be relatively minor. Given these variations, many of these tumors may not be carcinomas at all. Indeed, they are sometimes called well-differentiated tumors of undetermined potential (2). This name conveys the uncertain nature of the tumors, but it probably hasn't spared most patients additional surgery or post-operative iodine-131 therapy.

Robert D. Utiger, M.D.

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There is no effective treatment for anaplastic carcinoma of the thyroid: a summary of 50 years' experience at a single institution

McIver B, Hay ID, Giuffrida DF, Dvorak CE, Grant CS, Thompson GB, van Heerden JA, Goellner JR. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. *Surgery* 2001;130:1028-34.

SUMMARY

Background Approximately 2 percent of thyroid carcinomas are anaplastic carcinomas. They are by far the most aggressive type of thyroid carcinoma, and most patients die within a year after diagnosis. This retrospective study was undertaken to define the clinical characteristics and effects of treatment in all patients with anaplastic thyroid carcinoma seen at a single institution over a prolonged period.

Methods The records of all patients with anaplastic, undifferentiated, or poorly differentiated thyroid carcinoma treated at the Mayo Clinic between 1949 and 1999 were reviewed. Patients seen more than 30 days after diagnosis or who had received treatment elsewhere were excluded. The original tissue sections were reviewed by one pathologist, who confirmed the diagnosis of anaplastic carcinoma based on the presence of large or spindle-shaped cells, many mitotic figures, and necrosis. Immunohistochemical studies were done in some tumors to exclude lymphoma or medullary carcinoma of the thyroid. The patients' records were reviewed, and attempts were made to locate patients living at the time of last contact at the clinic.

Results The diagnosis of anaplastic thyroid carcinoma was confirmed in 134 patients during the 50-year interval, with no change in mean number per year (2.7) during this period. There were 80 women (60 percent) and 54 men (40 percent); their mean age was 67 years. The patients were followed until they died or to December 1999 (median, 3 months).

Six patients (4 percent) had a history of differentiated thyroid carcinoma (papillary carcinoma, 5 patients; follicular carcinoma, 1 patient) and had been treated with surgery and iodine-131 (I-131) an average of 10 years earlier (range, 2 to 32). At diagnosis, another 25 patients (19 percent) had foci of differentiated carcinoma and 27 patients (20 percent) had benign thyroid nodules. Overall, 58 patients (43 percent) had preexisting or coexisting thyroid disease.

130 patients (97 percent) presented with a rapidly enlarging neck mass; the others were diagnosed on the basis of lung or bone metastases. At diagnosis, most patients had extensive cervical lymphadenopathy, and 62 patients (46 percent) had distant metastases; 91 patients (68 percent) had distant metastases at some time. The primary tumor was usually large (mean, 7 cm; range, 2 to 16). The carcinoma was large-cell anaplastic carcinoma in 51 patients (38 percent), spindle-cell in 54 patients (40 percent), and mixed in 29 patients (22 percent).

Treatment consisted of palliation only in 5 patients (4 percent), and open biopsy followed by radiation therapy in 29 (22 percent) or chemotherapy in 4 (3 percent). Ninety-six patients (72 percent) underwent surgery; it was intended to be curative in 35 patients (26 percent), was debulking in 48 patients (36 percent), and was limited to biopsy in the remainder. The surgery varied from lobectomy to total thyroidectomy with extensive neck dissection; tumor resection was thought to be complete in 29 patients (22 percent). Most patients received radiation therapy after surgery, but only 1 patient had any decrease in tumor size. Chemotherapy was given to 12 patients to treat metastatic disease. Thirteen patients received the combination of surgery, radiation, and doxorubicin.

The median survival was 3 months; 13 patients (10 percent), all treated surgically, survived at least a year. Survival did not vary according to type of surgery or completeness of tumor resection. Postoperative radiation did not reduce the risk of local recurrence, but did delay it slightly. Among the 13 patients who received combination therapy, median survival was not increased, but more of them lived longer than 1 year than in the group as a whole (23 percent vs. 8 percent, $P = 0.19$).

Conclusion Anaplastic thyroid carcinoma is rapidly fatal, and few patients survive more than a year.

COMMENTARY

Anaplastic thyroid carcinoma is a terrible disease. Open biopsy may be needed to confirm the diagnosis, but whether surgery should be offered as treatment can be debated. At the Mayo Clinic, the proportion of patients who underwent curative or debulking surgery ranged from 35 percent in the 1960s to 100 percent in the 1970s, and it was 77 percent in the 1990s (the number of patients who declined surgery is not given). These

variations could represent changes in opinions about the efficacy of surgery, but they are more likely due to differences in the extent of disease at the time of diagnosis.

It does seem reasonable to offer surgery to patients who do not have extensive disease in the neck or metastatic disease, because a few do survive for more than a year. Offering radiation therapy or chemotherapy alone seems futile, but may be appropriate for patients who want some treatment. Offering radiation

therapy, chemotherapy, or both to patients who have had surgery seems almost as futile. A few patients may live a little longer, but at what cost? Ideally, any such treatments should be given as part of a clinical trial, or at least according to a standardized regimen, so that some knowledge and maybe some insights into the disease will be gained.

Robert D. Utiger, M.D.

The frequency of celiac disease is slightly increased in patients with chronic autoimmune thyroiditis

Volta U, Ravaglia G, Granito A, Forti P, Maioli F, Petrolini N, Zoli M, Bianchi FB. Coeliac disease in patients with autoimmune thyroiditis. *Digestion* 2001;64:61-5.

SUMMARY

Background Patients with autoimmune thyroid disease, particularly those with chronic autoimmune thyroiditis, are at increased risk for other autoimmune endocrine disorders, and perhaps also autoimmune disorders of other organs. The latter may include celiac disease (gluten-sensitive enteropathy). This study was undertaken to determine the frequency of serologic and anatomic evidence of celiac disease in patients with chronic autoimmune thyroiditis.

Methods The study subjects were 220 consecutive patients with chronic autoimmune thyroiditis, 50 euthyroid patients with one or more thyroid nodules, and 250 normal subjects (blood donors). The diagnosis of chronic autoimmune thyroiditis was based on unspecified clinical signs of hypothyroidism, a high serum thyrotropin (TSH) concentration, and a high serum concentration of thyroid microsomal, thyroid peroxidase, or thyroglobulin antibodies. Serum IgA tissue transglutaminase antibodies and IgA endomysial antibodies were measured in all study subjects, and serum IgG gliadin antibodies were measured in subjects with IgA deficiency. Subjects with high serum concentrations of any of the three celiac disease-related antibodies underwent duodenal biopsy. The presence of villous atrophy, crypt hyperplasia, and mucosal inflammation in the biopsies was considered diagnostic of celiac disease.

Results The 220 patients with chronic autoimmune thyroiditis included 196 women and 24 men. Seven (3 percent)

had serologic and anatomic evidence of celiac disease, as compared with none of the patients with thyroid nodules and 1 (0.4 percent) of the normal subjects (table).

Table. Characteristics and Results of Tests for Celiac Disease in Patients with Chronic Autoimmune Thyroiditis, Patients with Thyroid Nodules, and Normal Subjects.

	No.	Women/ Men	Mean Age (yr)	Anti-tTG*	Anti-Em	Anti-G [†]	Celiac Disease
Chronic autoimmune thyroiditis	220	196/24	48	7 (3.2%)	6 (2.7%)	6 (2.7%)	7 (3.2%)
Thyroid nodules	50	44/6	50	0 (0%)	0 (0%)	1 (2.0%)	0 (0%)
Normal subjects	250	210/40	42	1 (0.4)	1 (0.4%)	3 (1.2%)	1 (0.4%)

*tTG, tissue transglutaminase; **Em, endomysial; †G, gliadin.

All seven patients with chronic autoimmune thyroiditis who had high serum concentrations of tissue transglutaminase antibodies had histopathologic evidence of celiac disease. Two of them had clinical evidence of malabsorption, but both these patients and the other five patients had a normal body mass index. The one normal subject with a high serum concentration of tissue transglutaminase antibodies also had histopathologic evidence of celiac disease.

Conclusion Celiac disease is slightly more common among patients with chronic autoimmune thyroiditis, as compared with normal subjects or patients with thyroid nodules, and therefore they should be screened for celiac disease with measurements of serum tissue transglutaminase or endomysial antibodies.

COMMENTARY

Results comparable to these, demonstrating serologic and histopathologic evidence of celiac disease in a small percentage of patients with chronic autoimmune thyroiditis, have been reported before (1,2). Similarly, the frequency of chronic autoimmune thyroiditis is increased in patients with celiac disease (3).

Given the low frequency of celiac disease among patients with chronic autoimmune thyroiditis, the authors' conclusion that these patients should be screened for celiac disease by measuring serum tissue transglutaminase or endomysial antibodies seems inappropriate. If the serum concentration of one of the antibodies is high, should the patient be advised to have a duodenal biopsy or to eat a gluten-free diet? Is it

possible that the high serum antibody concentrations and even the villous atrophy and other abnormalities present on duodenal biopsy are due to hypothyroidism and will improve in response to thyroxine therapy? No one knows.

Whatever the associations, there are both similarities and differences between chronic autoimmune thyroiditis and celiac disease. Both are characterized by genetic susceptibility. They differ in that in celiac disease the autoimmune process is initiated by an external factor (dietary gliadin), and withdrawing it results in remission of the intestinal disease (and in some patients in remission of thyroid disease as well [3]). In chronic autoimmune thyroiditis, no external initiating factor has been identified, yet.

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Thyroid growth and function are increased in transgenic mice in which insulin-like growth factor I and its receptor are expressed in thyroid tissue

Clement S, Refetoff S, Robaye B, Dumont JE, Schurmans S. Low TSH requirement and goiter in transgenic mice over-expressing IGF-I and IGF-Ir receptor in the thyroid gland. *Endocrinology* 2001;142:5131-9.

SUMMARY

Background Many patients with acromegaly have thyroid enlargement, suggesting that insulin-like growth factor I (IGF-I), acting via IGF-I receptors, stimulates thyroid growth, just as it stimulates the growth of other tissues. In this study the gene for IGF-I, the gene for the IGF-I receptor, and both genes, were introduced into mice with a thyroid-specific promoter, so that the genes were expressed only in thyroid tissue. Thyroid structure and function were then determined in the three types of transgenic mice and normal (wild-type) mice.

Methods Transgenic mice were produced by injecting constructs of the promoter region of the bovine thyroglobulin gene and the coding regions of the human IGF-I gene or the IGF-I receptor gene into the pronucleus of fertilized mouse ova. Mice carrying each transgene were bred together to obtain mice bearing both transgenes. Expression of the two transgenes was verified by detection of IGF-I and IGF-I receptor messenger RNA and protein in thyroid tissue of these mice, but not in thyroid tissue from normal mice.

Thyroid weight and histology were determined in 7-, 12-, 16-, and 21-week-old mice. Thyroid iodine-131 (I-131) uptake was measured 48 hours after intraperitoneal injection of I-131 in 7-week-old mice. Serum thyroxine (T_4) and thyrotropin (TSH) were measured in control mice and mice fed methimazole in their drinking water for 7 weeks. There were 3 to 22 mice in the different groups. The numerical results given below were extrapolated from figures in the paper.

Results The body weight and behavior of the transgenic mice was similar to that of normal mice. The weight of the thyroid glands of 7-, 12-, and 16-week old IGF-I and IGF-I receptor transgenic mice was similar to that of normal

mice, but at 21 weeks it was slightly higher in the IGF-I receptor transgenic mice. In contrast, thyroid weight was increased (approximately 2 to 2.5 times) at all times in the mice with both transgenes. The histology and electron microscopy of the thyroid glands of the transgenic mice were normal, except that at 16 weeks the area of the follicles of the mice with both transgenes was increased and the number of follicular cells per mm^2 was slightly decreased, as compared with normal mice.

Thyroid I-131 uptake was similar in the IGF-I and IGF-I receptor transgenic mice and the normal mice, but was two times higher in the mice with both transgenes than in the normal mice. Serum T_4 concentrations were similar in 7-week-old IGF-I and IGF-I receptor transgenic mice and normal mice, but slightly higher in mice with both transgenes (approximately 3.6 $\mu\text{g}/\text{dL}$ vs. 3.1 $\mu\text{g}/\text{dL}$ [46 nmol/L vs. 40 nmol/L] in normal mice). Serum TSH concentrations at this time were slightly but not significantly lower in the IGF-I transgenic mice and lower in the IGF-I receptor and combined transgenic mice, as compared with normal mice (approximately 38, 25, 22, and 66 mU/L , respectively).

Administration of methimazole for 7 weeks reduced serum T_4 concentrations and raised serum TSH concentrations in all mice, but the changes were smaller in the mice with both transgenes. Administration of methimazole for 12 weeks resulted in proportionate increases in thyroid weight in all four groups of mice, but less depletion of colloid and less cellular hyperplasia in the IGF-I receptor transgenic mice and the mice with both transgenes as compared with normal mice.

Conclusion In mice, insertion of the genes for IGF-I and its receptor in thyroid tissue results in increased thyroid growth and function.

COMMENTARY

These results of activation of IGF-I and its receptor, especially both together, in thyroid tissue demonstrate that IGF-I stimulates not only thyroid growth but also thyroid secretion. The effects of the transgenes were somewhat counterbalanced by the decrease in TSH secretion in all three groups of transgenic mice, an effect that for the most part prevented thyroid growth and thyroid hypersecretion in all but the mice with both transgenes. These findings help to explain why goiter is more common than hyperthyroidism in patients with acromegaly (1).

In the patients, serum IGF-I concentrations and thyroid volume are positively correlated (2), and patients with larger goiters have lower serum TSH concentrations, but not higher serum T_4 concentrations, than patients with no goiter (1).

Thyroid tissue contains growth hormone receptors and IGF-I receptors, and given the presence of the former it is likely that IGF-I can be locally generated. Might locally generated IGF-I contribute to the formation and progression of diffuse or nodular goiter independent of excess growth hormone secretion? The results of Clement et al. suggest that is possible, but then what initiates local

production of IGF-I?

Robert D. Utiger, M.D.

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Postpartum thyroid disease is not associated with postpartum depression

Lucas A, Pizarro E, Granada ML, Salinas I, Sanmarti A. Postpartum thyroid dysfunction and postpartum depression: are they two linked disorders? *Clin Endocrinol* 2001;55:809-14.

SUMMARY

Background Approximately 5 to 10 percent of women who deliver babies have thyroid dysfunction within 12 months after delivery. Postpartum women are at increased risk for depression. Thyroid dysfunction, particularly hypothyroidism, is associated with some symptoms of depression, raising the question of whether postpartum thyroid dysfunction is associated with postpartum depression. This study evaluated the link between these two disorders in a large cohort of women followed for up to one year after delivery.

Methods The study subjects were 641 women (mean age, 28 years; range, 17 to 42) with no thyroid disease or diabetes mellitus. They were enrolled in the study between the 36th week of pregnancy and 4 days postpartum, and were evaluated at base line and at 1, 3, 6, 9, and 12 months after delivery; the number of women evaluated at the latter times ranged from 431 to 605. At each evaluation, the women completed the Beck Depression Inventory, were examined for thyroid enlargement and signs of thyroid dysfunction, and had measurements of serum thyrotropin (TSH) and free thyroxine (T₄). The inventory is a 21-item questionnaire in which each item is scored 0 to 3; scores of 17 to 20 indicate dysphoria, and scores ≥ 21 indicate depression. Women with scores ≥ 21 were evaluated by a psychiatrist, who used standard diagnostic criteria to confirm a diagnosis of depression. Postpartum thyroiditis was defined on the basis of transient biochemical abnormalities during the first six months after delivery: overt hyperthyroidism, subclinical hyperthyroidism (serum TSH concentration < 0.1 mU/L; normal, 0.4 to 4.0), overt hyperthyroidism, and subclinical

hyperthyroidism (serum TSH concentration > 4 mU/L). Women with hyperthyroidism were evaluated further to identify those with Graves' disease or a thyroid adenoma, as opposed to postpartum thyroiditis.

Results Overall, 56 women (11 percent) had postpartum thyroid disease, of whom 45 (8 percent) had postpartum thyroiditis, 8 (2 percent) Graves' hyperthyroidism, and 3 (1 percent) a thyroid adenoma. Sixty-one women (10 percent) had a score of ≥ 21 on the Beck Depression Inventory, of whom 11 (2 percent) were confirmed to have postpartum depression and 50 (8 percent) were not. Among the latter, 2 women were bereaved, 9 had anxiety, and 39 did not have enough symptoms of depression to fulfill the criteria for that diagnosis (14 had dysthymic disorder and 25 depressive disorder). There was no relation between postpartum thyroid disease and high Beck Depression Inventory scores or postpartum depression (table). The mean scores, which ranged from approximately 3 to 7 at the different times, were very similar in the women with postpartum thyroid disease and the normal women at all times.

Table. Rates of Depression in Normal Postpartum Women and Postpartum Women with Thyroid Disease.

	Normal Women (n=585)	Postpartum Women with Thyroid Disease (n=56)
BDI* Scores < 21	529 (90%)	51 (91%)
BDI Score ≥ 21 at any time	45 (8%)	5 (9%)
Postpartum depression	11 (2%)	0 (0%)

*BDI, Beck Depression Inventory.

Conclusion Women with postpartum thyroid disease are not at an increased risk for depression.

COMMENTARY

This study provides more evidence that postpartum thyroid disease is not associated with postpartum depression, although there is some evidence to the contrary (1,2). The differences in results are not surprising, because of variations in study design. These included numbers of women; how they were studied, and how often, with respect to both thyroid dysfunction and depression; the definitions of thyroid dysfunction and depression; and the time relationships between hyperthyroidism or hypothyroidism and depression.

The women with postpartum thyroiditis are not otherwise characterized in this paper, but they were earlier (3); 36 percent had hyperthyroidism and then

hypothyroidism, 22 percent had hyperthyroidism, and 42 percent had hypothyroidism. The overall frequency of postpartum thyroiditis (8 percent) was similar to that of other studies. These rates greatly overestimate the clinical importance of postpartum thyroiditis, because thyroid dysfunction in postpartum women is nearly always subclinical, detected only if the women are tested regularly. And the rates may be inflated because the biochemical abnormality is nothing more than a slightly low or high serum TSH concentration on one occasion. These facts, plus the lack of association of thyroid dysfunction of any type with depression or anything else, make screening for postpartum thyroid disease useless.

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Combining triiodothyronine with an antidepressant drug speeds improvement in patients with depression

Altshuler LL, Bauer M, Frye MA, Gitlin MJ, Mintz J, Szuba MP, Leight KL, Whybrow PC. Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. *Am J Psychiatry* 2001;158:1617-22.

SUMMARY

Background Patients with depression who have not responded well to tricyclic antidepressant drug therapy for several weeks may improve when their treatment is supplemented with thyroid hormone, in particular triiodothyronine (T_3), as compared with patients in whom treatment is continued with the antidepressant drug alone. This has been called T_3 -augmentation therapy. Initial treatment with a tricyclic antidepressant drug plus T_3 , called T_3 -acceleration therapy, also may be more effective than treatment with an antidepressant drug alone, but has been studied less well. This study was a meta-analysis of studies of T_3 -acceleration therapy.

Methods The criteria for identification of studies for this analysis were that the study was a double-blind, placebo-controlled trial in which patients with nonrefractory depression were treated with T_3 or placebo within five days after the initiation of antidepressant drug therapy and that a standardized scale was used to assess the severity of depression. Studies were excluded if there were fewer than five patients per treatment group, T_3 therapy was begun more than five days after antidepressant drug therapy was begun, and T_3 was given because the patient had not responded to the antidepressant drug.

Six studies were identified that met these criteria. The num-

ber of patients ranged from 15 to 30. The dose of T_3 was 20 to 25 μg daily in five studies and 25 to 62.5 μg daily in one study, and the T_3 or placebo treatment was initiated one to five days after the initiation of antidepressant drug therapy. The antidepressant drug was imipramine in five studies and amitriptyline in one study. Efficacy was determined after 21 to 28 days of combined antidepressant drug and T_3 or placebo treatment using the Hamilton rating scale for depression in all studies.

Results In five of the six studies the combination of an antidepressant drug and T_3 resulted in a statistically significantly more rapid reduction in the Hamilton rating scale score, as compared with antidepressant drug and placebo. For example, in one study the score fell by 50 percent after 11 days of treatment in the antidepressant drug and T_3 group and after 22 days of treatment in the antidepressant drug and placebo group. In most studies the fall in score was similar in the two groups by the end of the study period. The pooled analysis revealed the accelerated effect of combination therapy to be statistically significant ($P < 0.002$), and the effect of combination therapy increased as the proportion of women studied increased.

Conclusion In patients with depression, especially women, a low dose of T_3 accelerates the therapeutic response to therapy with a tricyclic antidepressant drug.

COMMENTARY

Patients with depression tend to have slightly higher serum thyroxine (T_4) concentrations than normal subjects. Their serum T_3 concentrations are not similarly increased, presumably due to decreased extrathyroidal conversion of T_4 to T_3 . Their daytime serum thyrotropin (TSH) concentrations are slightly low and the nocturnal surge in serum TSH concentrations is attenuated, but overall their serum TSH concentrations are not as low as might be expected given the increase in serum T_4 concentrations. These findings have been attributed to an increase in secretion of thyrotropin-releasing hormone and a decrease in secretion of somatostatin, each possibly caused by decreased serotonin activity in the brain (1).

How these changes relate to the therapeutic benefit of the combination of a tricyclic antidepressant drug and T_3 in

patients with depression is uncertain. This benefit has been noted not only in studies in which T_3 was added soon after the initiation of tricyclic antidepressant drug therapy, as summarized in this meta-analysis, but also in studies in which T_3 was added to tricyclic antidepressant drug therapy in patients who had not responded to more prolonged treatment with the latter alone, as summarized in another meta-analysis (2). (Addition of T_4 has not proven similarly effective, suggesting that intracerebral T_4 conversion to T_3 is impaired.) Depression is a chronic disorder, and the efficacy of addition of T_3 for a prolonged period is not known. In the studies in which T_3 was added early, its only benefit was to accelerate the response to the antidepressant drug. In the studies in which T_3 was added later, in patients with refractory depression, the duration of combined treatment did not exceed 28 days.

Today, most patients with depression

are treated with a selective serotonin reuptake inhibitor drug, such as fluoxetine, paroxetine, or sertraline. Some psychiatrists add T_3 to one of these drugs, as if it were a tricyclic antidepressant drug, but these combinations have never been systematically studied. From a hormonal perspective, the addition of 25 μg of T_3 daily is probably safe, but administration of higher doses should be discouraged.

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Thyroid hormone stimulates bone growth by increasing insulin-like growth factor I receptors in osteoblasts

Pepene CE, Kasperk CH, Pfeilschifter J, Borcsok I, Gozariu L, Zeigler R, Seck T. Effects of triiodothyronine on the insulin-like growth factor system in primary human osteoblastic cells in vitro. *Bone* 2001;29:540-6.

SUMMARY

Background Thyroid hormone is essential for normal skeletal growth in children, and it stimulates skeletal turnover in adults. In children and adults with hypothyroidism, the secretion of growth hormone and therefore systemic production of insulin-like growth factor I (IGF-I) are decreased, but the decreases may not be sufficient to account for the growth retardation in the children. Bone cells contain thyroid hormone receptors, and therefore thyroid hormone likely has direct effects on bone, which could include regulation of the production or action of IGF-I or IGF-II by bone cells. This study evaluated the effects of triiodothyronine (T_3) on the production of IGF-I and IGF-II, the production of IGF-I receptors, the proliferative action of IGF-I, and the production of several IGF-binding proteins by human osteoblast cells in vitro.

Methods and Results Osteoblasts were grown from explants of trabecular bone obtained at the time of knee or hip joint replacement of 6 women and 5 men aged 40 to 70 years who had osteoarthritis. The cultured cells were characterized as osteoblasts on the basis of their ability to secrete alkaline phosphatase and type I procollagen peptide in response to 1,25-dihydroxyvitamin D and to form osteoid that could be mineralized.

Incubation of osteoblasts with T_3 (10^{-9} to 10^{-7} mol/L) for 24 hours did not increase the cellular levels of IGF-I and IGF-II mRNA or the concentrations of IGF-I and IGF-II in the culture medium. In contrast, incubation of osteoblasts with the same concentrations of T_3 for 24 hours increased the cellular levels of IGF-I receptor mRNA in a dose-dependent manner; the highest T_3 concentration caused a twofold increase. The IGF-I binding capacity of the cells also increased two-fold, but there was no change in the affinity of the receptors for IGF-I. T_3 (10^{-7} mol/L) and IGF-I alone stimulated osteoblast proliferation, and the effect of IGF-I was potentiated by preincubation of the cells with T_3 . Incubation of the cells with T_3 (10^{-7} mol/L) increased the cellular level of IGF-binding protein-5 mRNA by 69 percent, but the levels of IGF-binding protein-3 and IGF-binding protein-4 did not change. IGF-binding protein-5 is thought to augment the action of IGF-I, whereas the other binding proteins may inhibit it.

Conclusion In osteoblasts, T_3 increases IGF-I receptor mRNA and IGF-I receptors and augments the ability of IGF-I to stimulate proliferation of the cells. T_3 also increases IGF-binding protein-5 mRNA, and presumably the production of IGF-binding protein-5, in the cells, which may potentiate the stimulatory effects of T_3 on bone.

COMMENTARY

Growth failure is one of the earliest, and may be the only, sign of hypothyroidism in children. The causes of the growth failure are both local and systemic. With respect to the local causes, the results of this study suggest that the absence of T_3 decreases the sensitivity of osteoblasts to IGF-I, by decreasing the production of IGF-I receptors and IGF-binding protein-5. These changes result in a decrease in the ability of IGF-I to stimulate the proliferation of these cells and therefore to stimulate new bone formation. The action of IGF-binding protein-5 to potentiate the action of IGF-I seems to be unique among the IGF-binding proteins, and indeed among hormone-binding proteins in general. That is because most hormone-binding proteins prevent egress of the hormone from serum, and if present in tissue decrease the concentration of free hormone and therefore the ability of the hormone to activate its receptors on cell membranes or within cells.

With respect to the systemic causes of growth failure in children with hypothyroidism, the most important abnormality is probably a decrease in 24-hour growth hormone secretion, manifested by a decrease in amplitude of pulses of GH secretion, especially at night (1). The decrease in GH secretion results in a decrease in serum IGF-I concentrations; in both children and adults with hypothyroidism the concentrations are about 50 percent of those in normal subjects of the same age (2). The decrease in GH secretion might also result in decreased IGF-I production in bone, exacerbating the effects of the decrease in IGF-I receptors presumed from the studies of Pepene et al. described above.

All these findings explain why children with GH deficiency and hypothyroidism grow poorly if treated with either thyroid hormone or GH alone, but instead must be given both.

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Correction

Opposite Changes in Plasma Homocysteine Concentrations in Patients with Hyperthyroidism and Hypothyroidism (July 2001:21). The plasma thyrotropin values were omitted from the table. The complete table is:

	Hypothyroid	Euthyroid	Hyperthyroid	Euthyroid
Plasma thyrotropin (mU/L)	65.5 (4.5-162)	2.5 (0.2-10.7)	0.01 (0.01-0.06)	1.0 (0.01-8.3)
Plasma free thyroxine (ng/dL)	0.4±0.3	1.3±0.3	3.8±1.2	1.2±0.4
Plasma homocysteine (μmol/L)	17.6±10.2	13.0±4.7*	10.7±2.5	13.4±3.3*
Plasma folate (ng/mL)	5.2±2.8	5.9±2.5	6.7±3.4	6.0±2.9
Plasma vitamin B ₁₂ (pg/mL)	453±253	410±161	462±188	472±198
Plasma creatinine (mg/dL)	0.9±0.2	0.8±0.2*	0.6±0.2	0.8±0.2*

Conversion factors; plasma thyroxine × 12.87 = pmol/L; plasma folate × 2.27 = nmol/L; plasma vitamin B₁₂ × 0.738 = pmol/L; and plasma creatinine × 88.4 = μmol/L.
*P<0.005, as compared with before treatment.