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SUMMARY

Background

It is well established that in an area with a sufficient iodine supply, thyroidal secretion contributes approximately 10% to 20% to the daily T_3 production. In the presence of iodine deficiency, this percentage can drastically increase. Therefore, the peripheral tissues of a normal subject are not entirely dependent on T_3 generated by conversion from T_4. In T_4-substituted athyreotic subjects, the lack of thyroid-generated T_3 is compensated for by higher serum T_4 values. Conversion of T_4 to T_3 is a variable process, depending on metabolic parameters. An example is the strong reduction of conversion due to fasting. Since the publication of a controversial article in the New England Journal of Medicine (1), the question of whether some athyreotic subjects could benefit from a mixture of thyroxine and triiodothyronine has been extensively studied, ending with the general conclusion that there is no clinical advantage to adding triiodothyronine to thyroxine treatment (2). The authors of the present article performed a large retrospective study trying to develop arguments that thyroxine treatment alone is not always sufficient.

Methods and Results

In this retrospective study covering the years 2002 to 2007, serum thyroid hormone parameters were studied in athyreotic subjects with a serum TSH between 0.4 and 4 mU/L. One third of these patients had had previous ^{131}I treatment. Patients with thyroid antibodies were excluded. Women predominated (81%) and 69% of the subjects were less than 60 years of age. The control subjects consisted of 3875 euthyroid subjects, investigated in the clinic for a nonfunctioning nodule of less than 2 cm in diameter. For statistical analysis nonparametric tests were applied.

In the control group, there were some minor and expected differences in FT_4 and FT_3 values according to sex and age. Over the range of 0.4 to 4 mU/L for serum TSH, FT_3 values did not change when plotted against the log TSH values.

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In the athyreotic group, mean serum TSH levels were similar to those in the euthyroid control group (1.2 vs. 1.4 mU/L). As expected, serum FT_4 values were slightly higher and FT_3 values slightly lower. As a consequence, the median individual FT_3:FT_4 ratio was lower in thyroxine-treated patients (0.24 vs. 0.32, P<0.001). There was a minimal but significant decrease of FT_3 in elderly male subjects.

Despite normal serum TSH levels, 15% of the athyreotic subjects had FT_3 values below the normal range and 7% had FT_4 values above the normal range. The results of the linear regression analysis between serum TSH and FT_4 were significantly steeper in T_4-treated subjects; in other words, in case subjects, larger changes in serum thyroxine were needed to adjust serum TSH than in control subjects. Interestingly, within the group of thyroxine-substituted patients the FT_3:FT_4 ratio decreased with higher administered doses, possibly reflecting an inhibition of deiodinase type 2 activity by circulating T_4 values.

CONCLUSIONS

Despite perfect control of serum TSH in athyreotic subjects (mean TSH, 1.2 mU/L, vs. 1.4 mU/L in control subjects; range 0.4 to 4), 15% of these patients had decreased serum T_3 levels, possibly indicating some thyroid hormone deficiency. Athyreotic patients had a lower FT_3:FT_4 ratio than control subjects. This ratio tends to decrease with a higher therapeutic dose of thyroxine. In patients, serum T_3 levels correlated with serum T_4, while in control, subjects serum T_3 levels remained constant despite differences in serum T_4. In addition, the pituitary TSH response to thyroxine was significantly different between the two groups, indicating a less refined feedback mechanism in athyreotic patients.

ANALYSIS AND COMMENTARY

The authors confirm the fact that the thyroid parameters of thyroxine-treated patients do not fully match those of the control subjects. In fact, serum FT_4 levels had to be higher in the treated patients in order to achieve similar FT_3 levels. This is well known. There was, however, an additional difference between patients and control subjects: In patients, the serum FT_3 values increased in close correlation with increasing serum FT_4 values, while in control subjects, serum FT_3 values remained constant and, thus, did not correlate with the serum FT_4 values. This finding may reflect the advantage of normal thyroid function over substitution therapy. The authors postulate that a relatively large fraction of athyreotic, T_4-treated patients, deemed to have satisfactory substitution according to serum TSH levels, may in fact have partial T_3 deficiency. This is possible, albeit not proven, since blood levels are not a clear reflection of intracellular T_3 pools. The circulating T_3 represents only 20% of the total T_3 pool. Clinical signs of thyroid deficiency were absent. We know that thyroid hormone effects are robust. In general, serum TSH needs to be 10 mU/L or more before clinical symptoms appear (3). This may reflect difficulties in finding sensitive criteria for hypothyroidism. At the present state of the art of therapy, one is tempted to conclude that these findings are interesting but clinically irrelevant. One word of caution: During pregnancy it is recommended that an abnormally low FT_3 be avoided. A technical remark: It is likely that during the 7 years of observation, several patients had repeated determinations of thyroid parameters, but this was not reported.

— Albert G. Burger, MD

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L-T_4 Treatment of Patients With Subclinical Hypothyroidism Can Partially Restore Cardiac Flow Reserve

Traub-Weidinger T, Graf S, Beheshti M, Ofluoglu S, Zettinig G, Khorsand A, Nekolla SG, Kletter K, Dudczak R, Pirich C. Coronary vasoreactivity in subjects with thyroid autoimmunity and subclinical hypothyroidism before and after supplementation with thyroxine. Thyroid. January 10, 2011 [Epub ahead print]. doi:10.1089/thy.2011-0183.

SUMMARY

Background

"Subclinical hypothyroidism" is not a disease but a combination of laboratory-test results that may be found in up to 10% of the population, and that has many possible causes. It is characterized by an elevated serum TSH level in the face of T_4 and T_3 levels in the normal range. Test–retest reliability for TSH is +/– 40% (1), and it is not uncommon for the TSH in patients with subclinical hypothyroidism to return to normal, although this can take 3 or more years to occur (2). On the other hand, overt hypothyroidism can develop in "euthyroid" patients with an elevated TSH: the risk ranges from 1.2% to 18% per year, depending largely on how high the TSH is (1). Patients with overt hypothyroidism are at increased risk for cardiovascular disease, but whether patients with subclinical hypothyroidism are at increased risk remains controversial, despite literally thousands of papers on the subject. A variety of physiological and biochemical tests have been used to study function and metabolism in the heart and various vessels in such patients, but the findings often have been discordant. The current paper addressed the microvascular function of the heart, using dynamic positron-emission tomography (PET) with ^{13}N-labeled ammonia, before and after infusing adenosine intravenously for 2 minutes, and then estimating myocardial vascular resistance (MVR), myocardial blood flow (MBF), and coronary flow reserve (CFR).

Methods

The 10 patients (28 to 58 years of age) initially recruited for the study had TSH levels ranging from 5 to 34 µU/ml (mean, ~17), and their TSH had been elevated for 2 to 9 months. Their mean levels of free T_4 and free T_3 were within the normal range, although they were significantly lower than the mean levels in 8 controls (38 to 60 years of age). The patients apparently had no major comorbidities, and were deemed to have Hashimoto's thyroiditis because they had positive anti-TPO antibodies (titers and duration of positivity not indicated). Initial baseline and adenosine-stimulated dynamic PET data were obtained in 9 patients, but only 8 received L-T_4 for 6 months. The dose was increased in 25-µg increments until the TSH level was between 1 and 2 µU/ml, which required doses of 150 to 500 µg/day. The 8 patients then underwent a second PET study. The peripheral infusion of adenosine does produce vasodilation of the coronary microvascular bed, but it can also transiently lower the systemic blood pressure and change the heart rate. MBF estimated from the dynamic PET images was combined with the heart rate and blood pressure 2 minutes after starting the adenosine infusion and used to correct the calculation of CFR and MVR.

Results

The mean myocardial parameters were provided for 8 controls and for 9 patients before L-T_4 treatment, but for only 8 patients after treatment. The mean adenosine stress MBF and corrected CFR values obtained before L-T_4 treatment were significantly lower in the 9 patients than in the 8 controls. Following 6 months of treatment with L-T_4, the mean CFR increased ~50% and the mean corrected CFR increased 24% (P = 0.043) in the 8 patients, but these mean values remained lower than the mean CFR of the 8 controls. No significant differences in regional CFR or stress MBF were found, indicating that no hemodynamically relevant stenosis was present.

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Conclusions

In 9 patients with slightly to substantially elevated TSH values, analysis of 13N-ammonia uptake indicated that several parameters of coronary microvascular function were significantly below control levels. In the 8 patents given 6 months of treatment with L-T_4, the mean corrected coronary blood flow improved but was not normalized.

ANALYSIS AND COMMENTARY

It is somewhat surprising that there was no analysis of pretreatment and posttreatment data for individual patients, since they would have served as their own controls. Nonetheless, the findings seem consistent with recent echocardiographic studies on myocardial microvascular function, and they raise the possibility that myocardial, smooth muscle, endothelial, neural, or stromal changes, rather than major vessel dysfunction, may be present in some patients. Hashimoto's thyroiditis is the commonest cause of subclinical hypothyroidism, but other possible causes include advanced age, obesity, polymorphisms in genes such as phosphodiesterase-8, and TSH-receptor blocking antibodies. An increased TSH level also can occur—usually transiently—after taking certain foods or drugs, or during recovery from subacute, painless or postpartum thyroiditis, or from nonspecific illness. Some of these diagnoses are difficult to confirm, but a positive TPOAb titer does not prove that Hashimoto's thyroiditis caused a patient's subclinical hypothyroidism: for example, in the patient who required 500 µg of L-T_4 for 6 months to normalize the TSH, a more obscure diagnosis (or noncompliance) might be possible. Furthermore, the wide range of TSH levels and the small number of subjects makes it difficult to know what to do with these results.

However, over the past 10 years or so, an upper limit of 10 µU/ml TSH for "watchful waiting" in subclinical hypothyroidism has become widely accepted. Patients whose TSH is consistently above 10 µU/ml are known to be much more likely to advance to overt hypothyroidism, and a recent analysis of 11 prospective studies indicates that such patients are at increased risk of coronary heart disease and death (3). In a patient who has symptoms consistent with hypothyroidism, which cannot be otherwise unexplained, and whose TSH is slightly above normal but below 10, it seems reasonable to try a "therapeutic trial" of L-T_4, recognizing that a favorable response does not prove that hypothyroidism was the cause. However, there are two clinical situations that require the physician's special attention when considering treatment of mild subclinical hypothyroidism. 1) In the pregnant patient, there is a clear consensus for giving L-T_4. 2) In contrast, L-T_4 treatment of elderly patients with mild subclinical hypothyroidism must be closely monitored. TSH levels increase with age regardless of anti-TPO positivity, and some studies have found that slightly elevated TSH levels are associated with increased survival to great age. The dose of L-T_4 given to elderly patients is of special concern, since a recent study found that over 40% of patients aged 65 were receiving overreplacement, and this group is especially at risk for cardiovascular and skeletal side effects (4).

— Stephen W. Spaulding, MD

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Gestational Hypothyroidism Is More Common Than Generally Acknowledged, But Testing for It Is Not Usually Performed

Blatt AJ, Nakamoto JM, Kaufman HW. National status of testing for hypothyroidism during pregnancy and postpartum. J Clin Endocrinol Metab. December 14, 2011 [Epub ahead print]. doi:10.1210/jc.2011-2038.

SUMMARY

Background

Knowledge of current national thyroid testing rates and abnormal results during pregnancy is limited. Hypothyroidism, overt and subclinical, is associated with adverse outcomes for pregnant women and their offspring. The aim of this study was to provide an analysis of the status of testing for hypothyroidism during pregnancy in a large national sample.

Methods

Quest Diagnostics has over 145 million patient encounters yearly with individuals from all states and the District of Columbia. For the present study, the authors extracted testing data from 502,036 pregnant and postpartum women (18 to 40 years of age) during the 36-month study period of June 1, 2005, through May 30, 2008; these samples were sent to Quest Diagnostics for routine pregnancy screening blood tests at the beginning of pregnancy and between 30 and 45 weeks thereafter. The testing rate for TSH was calculated as the number of pregnant women who had a TSH test result divided by the total number of women identified as being pregnant. Gestational week was based on the reported gestational age based on information provided by the woman's maternal serum screen. An assay-specific, trimester-specific reference interval of "within range" TSH concentration was 0.10 to 2.50 mIU/L during the first trimester, 0.55 to 2.75 during the second trimester, and 0.43 to 2.91 during the third trimester. The positivity rate for gestational hypothyroidism was calculated as the number of pregnant women who have gestational hypothyroidism divided by the number of pregnant women tested.

Results

Of the 502,036 women in the study, 117,892 (23%) were tested for gestational hypothyroidism by measuring TSH. Testing rates increased as the maternal age increased, Asian women had the highest testing rate (28%), whereas African American women had the lowest testing rate (19%). Women 35 to 40 years of age were 2.2 times as likely to be tested for gestational hypothyroidism as those who were 18 to 24. Women weighing over 275 lb (125 kg) were 1.3 times as likely to be tested for gestational hypothyroidism as those weighing between 100 and 124 lb (45.4 and 56.2 kg).

Of the pregnant women who were tested for gestational hypothyroidism, 15.5% of them had elevated serum TSH levels; 79% had TSH levels within the reference range for pregnancy. Multiple logistic-regression analysis was performed to examine the impact of age, race, and maternal weight on a woman's risk for gestational hypothyroidism. Women 35 to 40 years of age are 1.8 times as likely to have gestational hypothyroidism as those who are 18 to 24 years. In addition, women weighing over 275 lb are 2.5 times as likely to develop gestational hypothyroidism as those weighing between 100 and 124 lb. Asian women are almost five times as likely to have gestational hypothyroidism as African American women. A total of 24% (22,650 of 93,312) of women with TSH levels within normal range were also tested for gestational hypothyroxinemia; 0.2% had low FT_4 levels. In contrast, 33% (6072 of 18,291) of women with elevated TSH levels, were tested for FT_4; 2.4% of them (144 of 6072) had clinical hypothyroidism. Of the 18,291 pregnant women who had elevated TSH, 120 (0.7%) also received TPOAb testing; 78 (65%) women had a positive TPOAb result.

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Hispanic women had the highest TPOAb positivity rate, at 77.4%, whereas Asian women had the lowest rate at 45.5%. Only 1873 women with hypothyroidism returned for postpartum testing, and of those, 11.5% of them had postpartum hypothyroidism.

Conclusions

Gestational hypothyroidism is more common than generally acknowledged; testing is not common, and test selection is variable. There was a low rate of postpartum follow-up.

ANALYSIS AND COMMENTARY

The aim of the study was to analyze the status of testing for hypothyroidism during pregnancy in a large, national sample. During a 36-month study period (2005–2008), 502,036 samples were sent to the laboratory for routine pregnancy-screening blood tests at the beginning of pregnancy and between 30 and 45 weeks thereafter; serum TSH was also requested in 23% of them. A pregnant woman was found and included by having: (a) a rubella test, associated with the obstetric panel of tests typically ordered during the first prenatal visit; (b) a maternal serum screen result with both gestational age and race group recorded; and (c) any additional laboratory test performed at Quest Diagnostics between estimated weeks 30 and 45 of gestation. There are several problems with this study resulting, in my estimation, in erroneous conclusions.

The term gestational hypothyroidism is used without a definition, implying high serum TSH in pregnancy. I'm not aware of this term being used previously; my concern is that its use will create another literature controversy, similar to that for "gestational diabetes mellitus," which is defined as first recognition of glucose intolerance during pregnancy. Therefore, if the same criterion is used for "gestational hypothyroidism," women previously diagnosed with thyroid dysfunction should be excluded. It appears that the authors have assumed that women were euthyroid before conception, since they consistently used the phrase "to develop gestational hypothyroidism" (e.g., "Women ages 35 to 40 yr are 1.8 times as likely to develop gestational hypothyroidism as those ages 18 to 24 yr.").

In 23% (117,892) of women, the total serum samples were tested for gestational hypothyroidism by measuring TSH. The authors stated that "This study describing the testing results from a large, national population of over one-half million pregnant women provides unique insights into the use of thyroid testing in obstetrical care." On the contrary, the authors do not provide information for the reasons or indications by the health care professional for ordering a serum TSH in their population. Routine thyroid testing was not mandated at the time of the study and is not at the present recommended by the American College of Obstetricians and Gynecologists (ACOG). The only available patient information to the authors was age, race, weight, and gestational age. Most of the requested serum TSH testing was included in the initial pregnancy-screening tests. The authors assumed, therefore, that serum TSH was ordered as a screening test, without considering the possibility that of those tested women, some were hypothyroid on replacement therapy before conception. It may be argued, therefore, that the majority of requested serum TSH tests were in women who were on thyroid-replacement therapy; the reported incidence of "high TSH values" early in pregnancy in hypothyroid women on thyroid-replacement therapy antedating pregnancy may be as high as 40% to 50% (1) as contrasted with the 2% to 4% in the general population after excluding women with known thyroid disease prepregnancy; the same conclusion could be reached for their high incidence of overt hypo-

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thyroidism (2.5%), as compared with 0.2% to 0.4 % in the literature (2).

The authors stated: "Therefore, it is surprising that, in pregnant women with documented hypothyroidism, a low percentage (0.7%) is tested for the presence of TPO Ab. Given the high rate of TPO Ab positivity (65%) in women with gestational hypothyroidism, TPO Ab testing should be considered for all women with gestational hypothyroidism." The reason for this recommendation is not given. The fact that very few TPOAb tests were requested in their population of women with gestational hypothyroidism suggests to me that the majority of their hypothyroid population indeed already had thyroid dysfunction and that there were no clinical indications for serum TPOAb testing. Furthermore, recently published clinical guidelines (3) do not recommend routine screening for TPOAb in pregnant women with elevated serum TSH.

Finally, the authors' conclusions that "gestational hypothyroidism is more common than generally acknowledged; testing is not common, and test selection is variable" are misleading, since no information about antepartum clinical status is given. The more plausible alternative hypothesis that could better explain their results is that serum TSH, with or without serum FT_4, was ordered by health care professionals in order to assess thyroid status early in pregnancy in women who were receiving thyroid-replacement therapy. No information is given about follow-up TSH results later in pregnancy.

— Jorge H. Mestman, MD

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How Safe Is Glucocorticoid Treatment In Graves' Orbitopathy?

Marcocci C, Watt T, Altea MA, Rasmussen AK, Feldt-Rasmussen U, Orgiazzi J, Bartalena L. Fatal and non-fatal adverse events of glucocorticoid therapy for graves' orbitopathy: a questionnaire survey among members of the European Thyroid Association. Eur J Endocrinol 2012;166:247-53. Epub November 4, 2011.

SUMMARY

Background

The use of high-dose glucocorticoid therapy is well established for the treatment of severe autoimmune diseases, such as systemic lupus, multiple sclerosis, and graft-versus-host rejection. For approximately 25 years, it has also been used to treat severe forms of Graves' ophthalmopathy, and at present, it is in fact the preferred method of treatment in Europe. There is some suggestive evidence that intravenous (IV) administration is superior to oral treatment with glucocorticoids. The adverse effects of these two methods of treatment need, therefore, to be analyzed with great care. This was the purpose of the present article, which is based on a questionnaire survey among the members of the European Thyroid Association (ETA).

Methods and Results

The questionnaire was sent to all ETA members, including many nonclinicians; 128 members responded, 115 of whom were using glucocorticoids to treat Graves' ophthalmopathy. Of these 115 respondents, 72% of them use IV methylprednisolone. Once-weekly infusion was preferred by 60% of the physicians, but others chose to treat up to three times per week. In 80% of the cases, the mean dose of infused steroid was 0.5 to 1 g and the total amount varied between 4.5 g and a maximum of 12 g. The duration of the infusion was not specified. For the oral route, most clinicians used a fixed initial dose between 40 and 75 mg of prednisone per day. Tapering of the treatment was started after 2 weeks, and patients were treated on average for 3 months. The mean total dose was 2.4 g.

The percentage of adverse effects was much higher with the oral treatment than with IV administration (82% vs. 39%), but with the IV treatment, the rate of fatal adverse events was very high. With the oral treatment, nonfatal adverse effects were cardiovascular events, three cerebral vascular events, and increases in liver enzymes to four times above normal values; the remaining side effects were hyperglycemia, weight gain, facial changes and others. Nevertheless, 2 patients who were orally treated died of cerebrovascular events.

Of the IV-treated patients, 32 suffered from side effects, 27 of which were severe — cardiovascular (10), cerebrovascular (5), acute liver failure (3), autoimmune encephalitis (1), and liver enzymes more than four times above normal. Seven patients died, 4 of acute liver failure, 2 of a cerebrovascular events, and 1 of pulmonary embolism. Three of them had no comorbidities.

Conclusions

Intravenous glucocorticoid treatment of Graves' ophthalmopathy is the preferred treatment in Europe. The adverse side effects were less frequent than with the oral treatment, but more severe, since several lethal complications were reported, even among young and middle-aged persons with no other comorbidities. With the exception of one case, the deceased patients received a large total dose of glucocorticoids, exceeding 8 g. Oral treatment is not devoid of lethal adverse effects, since 2 lethal cases, due to cerebrovascular events, have been reported, including one 32-year-old patient with no comorbidities who initially received 60 mg per day and a total dose of 2.3 g. The authors suggest that IV treatment should not exceed a total dose of 8 g, that glucocorticoids should be given as a slow infusion, and that not more than one infusion per week should be performed.

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ANALYSIS AND COMMENTARY

Over a very short period, two articles appeared on this subject. The article under discussion reflects the results of a questionnaire addressed to many well-known European thyroidologists. It probably includes the majority, if not all, of the severe adverse effects of this treatment, but we do not know the time span over which these observations were reported. The second open question concerns the frequency of these adverse effects, since the article reports the percentage of endocrinologists who have seen adverse effects, but it does not state the frequency of these events as compared with the total number of patients treated by each individual endocrinologist. The largest study on the topic, including more than 800 subjects, states a frequency of less than 1% (1). This is important to realize, particularly in relation to the article being reviewed in the next article in this issue of *Clinical Thyroidology* by Jerry Hershman (2). This article is a careful evaluation of the hepatic immune status before treatment. No adverse effects were observed even though treatment was given as an IV pulse.

Yet hepatic adverse effects are not the only complications. In the European study, nine lethal cases are reported, four due to acute liver failure, four to a cerebrovascular event, and one to pulmonary embolism. It is particularly important to realize that from the two patients who died while undergoing oral treatment, one had no comorbidity and died at the age of 32 years from a cerebrovascular event. Three patients who died while undergoing IV treatment had no preexisting comorbidities.

The recommendations of the European survey cannot lead to ultimate answers, since they are based on common sense rather than on scientific data. Nevertheless, it is probably wise to remember that this treatment should be reserved for severe cases of Graves' ophthalmopathy, that the total IV dose should not exceed 8 g, that the infusion should not be more frequent than once a week, and that the glucocorticoid should be given as an infusion over 1 hour or more. In addition, clinical and biochemical surveillance is strictly indicated.

— Albert G. Burger, MD

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Methylprednisolone Pulse Therapy for Graves' Orbitopathy Did Not Cause Hepatotoxicity in 30 Patients

Wichary H, Gasińska T. Methylprednisolone and hepatotoxicity in Graves' ophthalmopathy. Thyroid 2012;22:64-9. Epub October 26, 2011.

SUMMARY

Background

Graves' orbitopathy (GO) varies in severity from minimal to severe. Corticosteroids are used as first-line therapy in patients with active moderate to severe orbitopathy. In recent years, intravenous methylprednisolone has become the standard therapy, but the dose schedule has varied among different centers. Severe liver toxicity has been reported as a side effect of this therapy. The aim of the current study was to assess changes in liver function related to this therapy.

Methods

The study enrolled 30 patients with moderate to severe active GO who had been euthyroid for at least 4 months while undergoing methimazole therapy. None of the patients had received radioiodine before the pulse therapy with methylprednisolone (MPRED). The activity of the GO was assessed by a clinical activity score, and the severity was estimated by the modified NOSPECS classification (1). Clinical evaluation of the orbit was performed to assess improvement. The course of MPRED was a cumulative dose of 8 g given intravenously over a 4-week period, but the specific dosing regimen was not stated. Patients had detailed studies of liver function, lipids, neoplastic markers, and hepatitis serology before and shortly after MPRED therapy.

Results

All patients had improvement in soft-tissue swelling, clinical activity score, and eye movements, but no improvement in proptosis after MPRED therapy. There were small decreases in total serum proteins, gamma globulin, fibrinogen, alkaline phosphatase, and direct bilirubin and no significant changes in liver enzymes after MPRED therapy. Total, LDL, and HDL cholesterol increased with therapy. There were no significant changes in hepatitis serology. Seven patients had evidence of past hepatitis B infection, but there was no new active infection related to the therapy.

Conclusions

In this study of 30 patients treated with high-dose intravenous methylprednisolone, there was no deterioration of hepatic function or reactivation of hepatitis B.

ANALYSIS AND COMMENTARY

Although the evaluation of liver function was performed very carefully and completely, the number of subjects was too small to exclude the possibility of severe liver dysfunction related to the therapy. In a study of 800 patients treated with intravenous pulses of MPRED for GO with cumulative doses ranging from 3 to 24 g, 7 patients had severe liver damage that was fatal in 3 (2). In a recent review (3) of MPRED therapy for GO and its toxicity in 1045 patients (which also included the 800 patients studied by Marino et al. (2) as well as single case reports), severe liver toxicity was reported in 15 (1.4%). The data suggest that it would take a study of several hundred patients to find a few with significant liver toxicity related to the MPRED therapy. Nevertheless, the current thorough study of 30 patients indicates that mild liver-function abnormalities are not a common side effect of this therapy. The results suggest that careful studies of liver function should be performed before using MPRED therapy for GO and that this therapy should be avoided in patients with significant hepatic dysfunction.

— Jerome M. Hershman, MD

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Clinical THYROIDOLOGY
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Prophylactic Central-Lymph-Node Dissection in Patients With Papillary Thyroid Cancer Reduces the Need for Reoperation in the Central Compartment

Popadich A, Levin O, Lee JC, Smooke-Praw S, Ro K, Fazel M, Arora A, Tolley NS, Palazzo F, Learoyd DL, Sidhu S, Delbridge L, Sywak M, Yeh MW. A multicenter cohort study of total thyroidectomy and routine central lymph node dissection for cN0 papillary thyroid cancer. Surgery 2011;150:1048-57.

SUMMARY

Background

There is continuing controversy about whether prophylactic central-lymph-node dissection (CLND) is beneficial for patients who are undergoing an initial thyroidectomy for papillary thyroid cancer without clinically apparent lymph-node involvement. This article reports a three-center retrospective study that addresses this issue.

Methods

The study included 606 patients undergoing total thyroidectomy for papillary thyroid cancer (PTC) between 1995 and 2009. There were 396 patients from Australia, 182 from the United States, and 28 from the United Kingdom. In Australia, routine ipsilateral CLND was adapted after 2003. Patients qualifications included age of at least 16 years, PTC >10 mm on final histology, no evidence of lymphadenopathy on clinical examination or preoperative ultrasound, no lateral neck dissection at surgery, and no distant metastases. Patients were divided into two groups: 347 had complete thyroidectomy only (group A) and 259 had complete thyroidectomy with CLND (group B).

Results

The characteristics of age, sex, tumor size, multifocal tumors, and TNM stages were similar in the two groups, but there were more patients with vascular invasion who had CLND and the mean follow-up was shorter in this group (32 months vs. 50 months for group A, P = 0.002). The mean number of lymph nodes removed was 7, and 49% of those with CLND had nodal disease on histology. On the basis of lymph-node involvement in the CLND cohort, 25 patients (10%) were upgraded from stage I or II to stage III. Temporary hypocalcemia occurred in 9.7% of group B and 4.1% of group A (P = 0.026). There were no other differences in the rates of complications in the two groups.

Ninety-eight percent of the patients had ^{131}I ablation. Stimulated thyroglobulin (Tg) and the mean cumulative doses were similar in the two groups. The mean final stimulated Tg at 12 months of follow-up was similar in the two groups; in subgroup analysis, patients with T2 tumors in group A had a higher mean stimulated Tg than that in group B. In group A, 8.1% required reoperation for recurrence while only 5% of group B required reoperation. Having prophylactic CLND dissection significantly decreased the risk of reoperation in the central compartment, with a hazard ratio of 0.11 (95% CI, 0.1 to 0.8). It was calculated that 20 routine CLND procedures were required to prevent 1 case of central compartment reoperation for recurrence.

Conclusions

Routine CLND in patients without clinically apparent central node disease reduces the need for reoperation in the central compartment.

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ANALYSIS AND COMMENTARY

The debate about the benefit of prophylactic CLND in patients with stage 1 or 2 disease rages on. It should be noted that the current ATA guidelines do not recommend for or against prophylactic CLND in low-risk patients (1). Although the authors of this study recommend prophylactic CLND, the study is not definitive. The main reason for this is that it is a retrospective study in which there was no randomization. The patients who had CLND were from a more recent time, generally after 2002. The fact that group B had more vascular invasion could represent selection bias based on frozen section; there was no statement about this.

The main reason for not recommending prophylactic CLND is fear of unnecessary complications from the procedure. Although there was more temporary hypocalcemia in group B, there was no difference in permanent hypocalcemia; this was attributed to routine parathyroid gland autotransplantation. There was no significant difference in rates of recurrent nerve injury between the two groups, possibly attributable to the fact that the operations were performed in tertiary-care centers by high-volume surgeons. The argument in favor of the prophylactic CLND is twofold. First, it is difficult to detect nodes in the central compartment by ultrasound (2). Second, there may be a benefit resulting from reduction of recurrence, as shown in this study. However, to settle this contentious matter, a prospective, randomized trial will be necessary.

— Jerome M. Hershman, MD

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Can Survival Be Improved in Some Patients With Anaplastic Thyroid Cancer?

Akaishi J, Sugino K, Kitagawa W, Nagahama M, Kameyama K, Shimizu K, Ito K, Ito K.
Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma.
Thyroid 2011;21:1183-9. Epub September 21, 2011.

SUMMARY

Background

Patients with anaplastic thyroid carcinoma (ATC) have a poor prognosis, with a median life expectancy of <6 months (1,2). It is unclear why a few patients survive for somewhat long times. An analysis of the outcome of a relatively large number of 100 patients with anaplastic thyroid cancer at a single center was used to identify prognostic factors and treatment outcomes of these patients.

Methods and Results

This was a retrospective chart review study at a single referral center. Review of medical records between 1993 and 2209 revealed 100 patients with a diagnosis of ATC, based on a combination of clinical findings and a fine-needle aspiration biopsy or an open biopsy. There were 80 women and 20 men, with a median age at diagnosis of 68 years (range, 41 to 90). The initial extent of disease of these patients was 11% stage IVA, 31% stage IVB, and 58% stage IVC. Seventy patients underwent surgical treatment, with 24 undergoing complete resection. Seventy-eight patients received radiotherapy, with 58 receiving a total dose of ≥40 Gy. Twenty-seven patients received chemotherapy, and 15 patients received multimodal therapy (surgery, radiotherapy, and chemotherapy). Survival rates by stage at 1 year were 72.7% (stage IVA), 24.8% (stage IVB,) and 8.2% (stage IVC). Poor prognostic factors determined after multivariate analysis were age ≥70 years, white-cell ≥10,000 mm3, extrathyroidal invasion, and distant metastases. Survival after complete resection was better than after incomplete resection or no resection. In addition, radiation doses ≥40 Gy were associated with longer survival. There was long-term survival in 14 patients. Death was related to anaplastic thyroid cancer in 81 patients (21 with local progression, 55 with distant disease, and 3 with both). There were 3 deaths from other diseases, and 2 deaths from unrelated causes.

Conclusions

The prognosis for anaplastic thyroid cancer is poor. This study suggests that surgical treatment, including debulking neck tumors, improved local control and survival. Postoperative radiotherapy has been recommended to control local disease (3). This study suggests that there is a significantly prolonged survival, but only when associated with radiation doses ≥40 Gy. Chemotherapy was more difficult to assess because the agents used changed from year to year. There was no clear improved survival with any one of the regimens used. There was no survival benefit with the addition of paclitaxel to other chemotherapy. Although the overall outcome of ATC remains poor, treatment of early-stage disease with combination surgery, high-dose radiation and chemotherapy may improve the outcomes of a small number of patients with this diagnosis.

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ANALYSIS AND COMMENTARY

The 2009 ATA thyroid nodule and cancer guidelines did not address in detail the recommended treatment(s) for anaplastic thyroid carcinoma. At the time of this writing, there were few studies with large numbers of patients with an improvement in life expectancy. Recently, there have been several studies (2-4) with sufficient numbers of patients to allow for management recommendations. This study, with the data from a 50-year review at the Mayo clinic (1), suggests that surgery alone is ineffective to improve survival. Multimodal therapy with radiotherapy ≥40 Gy or by intensity-modulated radiotherapy (IMRT) improves survival of patients with local disease. A recent study at the Mayo clinic (4) suggests that for local disease (stages IVA and IVB) an aggressive approach combining IMRT with radiosensitizing therapy and adjuvant chemotherapy improves survival. There is an emerging concept that localized disease (with no evidence of gross invasion or distant metastases) should be treated aggressively rather than providing only palliative care for all patients with ATC. Currently, there is no standardized treatment protocol for ATC, but evidence-based guidance is coming soon. Dr. Robert Smallridge, chair of the guideline committee, anticipates that the ATA guideline for the management of anaplastic thyroid carcinoma will be published in 2012.

— Stephanie L. Lee, MD, PhD

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You Do Not Have to Wait Three Months to Repeat the FNAB When It Is Nondiagnostic or Insufficient

Singh RS, Wang HH. Timing of repeat thyroid fine-needle aspiration in the management of thyroid nodules. Acta Cytol 2011;55:544-8. Epub December 9, 2011.

SUMMARY

Background

When the results of a thyroid fine-needle aspiration biopsy (FNAB) are reported as unsatisfactory or nondiagnostic, it is recommended that a repeat biopsy be performed. The Bethesda system recommends that this be done no sooner than 3 months after the initial aspiration because reparative and reactive changes from the FNAB could lead to false positive interpretations (1). The purpose of the present study was to determine whether this 3-month interval is necessary in order to obtain accurate results on a repeat FNAB.

Methods

Thyroid FNABs performed at the Beth Israel Deaconess Medical Center between January 2006 and December 2008 were reviewed; 307 patients had more than one FNAB of the same lesion. The initial specimen was nondiagnostic in 138 and suboptimal in 108 patients. The repeat FNAB was evaluated and compared with regard to the initial diagnosis and the timing for doing the repeat FNAB.

Results

Sixty-three percent of the patients had the repeat FNAB less than 3 months after the initial one. The percentage of nondiagnostic repeat FNABs done less than 3 months and those done more than 3 months after the initial FNAB was 17% in both cases. Overall, 53% of the repeat FNABs yielded an adequate diagnostic specimen. Of the repeats, 52% and 54% were adequate in those done less than 3 months and those done more than 3 months after the initial FNA, respectively. Of the 138 initial nondiagnostic specimens, 24% were nondiagnostic on repeat FNAB, 31% were suboptimal, and 45% were adequate. Of the 108 initial suboptimal specimens, 11% were nondiagnostic on the repeat, 23% were suboptimal, and 66% were adequate. For suboptimal specimens on repeat FNAB, the percentage was 28% for aspirations done less 3 months after the initial FNAB and 24% for those done more than 3 months later.

Eighty-one of the 307 patients had a subsequent thyroidectomy after the repeat FNAB. Based on benign pathology, 16% of the repeat FNABs were considered false positive when the repeat FNAB was performed less than 3 months after the initial FNAB and 12% were false positive when the repeat FNAB was done more than 3 months later.

Conclusions

The diagnostic yield and accuracy of repeat FNAB is independent of the time interval between procedures but may be related to the original FNAB diagnosis.

ANALYSIS AND COMMENTARY

When the initial diagnosis indicates that a repeat FNAB is indicated because of an insufficient or nondiagnostic result, the data of this retrospective study show that it is not necessary to wait 3 months or longer to perform a repeat FNAB in order to avoid a false positive result. Unfortunately, the data also show that repeat FNAB is likely to yield a nondiagnostic or suboptimal result in about half of the cases that had these findings on the initial specimen. This is consistent with my personal experience. Some of the nodules seem reluctant to provide good material, no matter

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who does the FNA. In a Korean study of 4077 FNAB, 16% yielded inadequate samples (2). The factors predisposing to inadequate samples were cystic nodules, macrocalcifications, and operator inexperience. In the current study, there was no analysis based on the experience of the operator or the ultrasound characteristics of the nodule. Nevertheless, the data indicate that first nondiagnostic FNABs predispose to second nondiagnostic biopsies. Although this is disappointing, it gives reassurance that the fault may lie within the nodule rather than the operator.

— Jerome M. Hershman, MD

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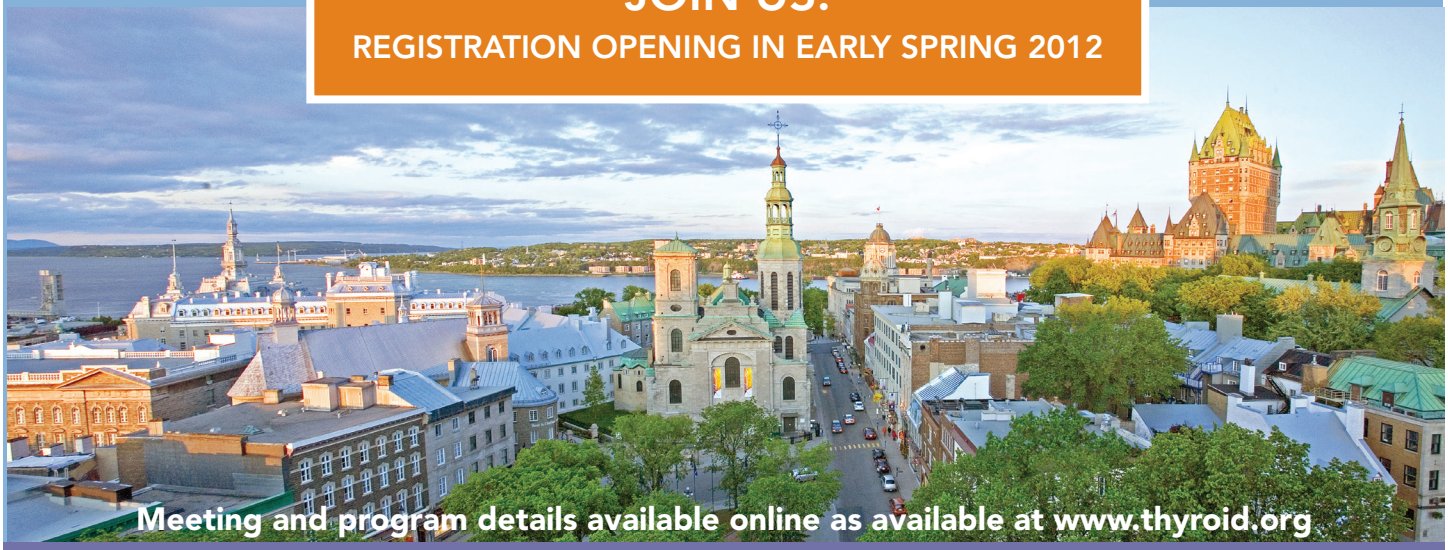

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