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Clinical THYROIDOLOGY

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FIVE-YEAR SURVIVAL IS SIMILAR IN THYROID CANCER PATIENTS WITH DISTANT METASTASES PREPARED FOR RADIOACTIVE IODINE THERAPY WITH EITHER THYROID HORMONE WITHDRAWAL OR RECOMBINANT HUMAN THYROTROPIN

Tala H, Robbins R, Fagin JA, Larson SM, Tuttle RM. **Five-year survival** is similar in thyroid cancer patients with distant metastases prepared for radioactive iodine therapy with either thyroid hormone withdrawal or recombinant human **TSH.** J Clin Endocrinol Metab. May 11, 2011 [Epub ahead of print].

BACKGROUND

Randomized trials have demonstrated that radioactive iodine (RAI) ablation of thyroid remnants is equally facilitated by withdrawal from thyroid hormone, inducing hypothyroidism, and by administration of recombinant human thyrotropin (rhTSH) (1,2). Reports have suggested that small-volume local nodal disease identified incidentally after remnant ablation appears to be effectively treated by either withdrawal or rhTSH preparation (2,3). This is a retrospective study to determine whether there is a difference in the short-term survival of patients with iodine-avid thyroid cancer metastatic to bone or lung (American Joint Committee on Cancer stage IV) and treated with RAI after either TH-WD or rhTSH administration.

METHODS

This 17-year retrospective study, conducted from 1993 through 2010, involved 175 patients with differentiated thyroid cancer with iodine-avid metastatic disease to bone (28%), lung (52%) or both (19%). Patients were excluded if the tumor was anaplastic or not iodine-avid or if there was metastatic disease to other organs. Patients were also excluded if there was inadequate follow-up or other malignancies or if the patients was <20 years old.

All patients treated with RAI for distant metastases were placed on a low-iodine diet and underwent formal whole-body and blood RAI clearance dosimetry studies to calculate a dose that delivered <2 Gy to the bone marrow and had less than 80 mCi whole-body retention at 48 hours. Thirty-eight patients had received one or more doses of RAI after thyroid hormone withdrawal prior to referral to the authors' center. Patients treated before 1998 received RAI after withdrawal; starting in 1998, when rhTSH became commercially available,

FIVE-YEAR SURVIVAL IS SIMILAR IN THYROID CANCER PATIENTS WITH DISTANT METASTASES PREPARED FOR RADIOACTIVE IODINE THERAPY WITH EITHER THYROID HORMONE WITHDRAWAL OR RECOMBINANT HUMAN THYROTROPIN

patients were treated on the basis of individual patient and physician discussions. All rhTSH treatments were performed with a four-dose schedule that included two doses before a blood and whole-body dosimetry protocol to determine RAI activity and a second set of 2 rhTSH injections before RAI therapy. Thirty-five patients were treated only after thyroid hormone withdrawal, 58 patients were treated only with rhTSH, and 82 patients had thyroid hormone withdrawal with one or more initial treatments and subsequent RAI activities administered after rhTSH.

RESULTS

The clinical characteristics of the patients were not different when segregated by method of preparation for RAI therapy. There was no different in age, sex, evidence of metastases at diagnosis of thyroid cancer, distribution of the distant disease, size of lung metastases, or multiplicity of bone metastases. Patients who were prepared for RAI by thyroid hormone withdrawal only were treated twice, on average, with a cumulative median dose of 522 mCi. Patients prepared for RAI by rhTSH only were also treated twice, on average, with a cumulative median dose of 408 mCi. The patients who were treated with both thyroid hormone withdrawal and rhTSH received, on average, four doses of RAI, with a cumulative median dose of 967 mCi. But the median activity per dose was higher in patients prepared

with rhTSH only (median, 263 mCi; range, 30 to 514) than in patients prepared with thyroid hormone withdrawal only (median, 200 mCi; range, 30 to 480; P = 0.038). Despite the difference in cumulative dose or individual administrations, there was no significant difference in overall survival between patients who were treated with RAI by withdrawal only, rhTSH only or withdrawal followed by rhTSH after a median of 5.5 years (range, 0.8 to 21). In a multivariate analysis including clinicopathological features and methods of preparation, only age at diagnosis was an independent predictor of overall survival. Examining a subset of 73 patients who had only micrometastases in the lung, there was no difference in the survival curves (P = 0.79) whether they were prepared by rhTSH only (32.9%), thyroid hormone withdrawal only (21.9%) or thyroid hormone withdrawal followed by rhTSH (45.2%). The median survival of patient with micrometastases in the lung was 12.5 years.

CONCLUSIONS

This is the first report to show a similar 5-year overall survival rate in patients with thyroid cancer who had iodine-avid distant metastases in the lung and bone when prepared by thyroid hormone withdrawal or rhTSH with dosimetry determined RAI activity treatments. When examined by multivariate analysis, the method of preparation for RAI had no impact on overall survival.

This study confirms clinical observations that when rhTSH was used because either TSH levels could not be elevated or hypothyroidism was thought to be too clinically risky, there is some clinical benefit to RAI therapy of thyroid cancer with metastases (4). It is important to understand that rhTSH is not approved by the Food and Drug Administration for the treatment of metastatic thyroid cancer. Further caution must be used because the average RAI activity administered was higher when rhTSH preparation was used as compared with thyroid hormone withdrawal. The higher dose with rhTSH was due to the more rapid clearance of RAI in the nonhypothyroid state, allowing for higher activity to be administered before the limits to blood and whole body were achieved. This higher dose very likely resulted in a higher dose delivered to the iodine-avid lesions than with thyroid hormone withdrawal.

Clinically, it is exciting to think that patients with distant disease can be treated with less discomfort from hypothyroidism, but ultimately, I think that our standard empirical doses of RAI for distant *continued on next page*

FIVE-YEAR SURVIVAL IS SIMILAR IN THYROID CANCER PATIENTS WITH DISTANT METASTASES PREPARED FOR RADIOACTIVE IODINE THERAPY WITH EITHER THYROID HORMONE WITHDRAWAL OR RECOMBINANT HUMAN THYROTROPIN

disease possibly will not result in the same results as achieved at this premier institution for thyroid cancer care. I cannot conclude that patients with iodine-avid distant disease will be adequately treated with rhTSH and empirical doses of RAI, but it is fair to say that a four-dose rhTSH-stimulated dosimetrydetermined treatment with RAI for a patient with RAIavid metastatic disease appears to be a reasonable alternative to traditional thyroid hormone withdrawal RAI treatments.

- Stephanie L. Lee, MD, PhD

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HYPERTHYROIDISM DUE TO HCG OCCURS IN 2% OF CASES OF GESTATIONAL TROPHOBLASTIC DISEASE

Walkington L, Webster J, Hancock BW, Everard J, Coleman RE. **Hyperthyroidism and human chorionic gonadotrophin production in gestational trophoblastic disease.** Br J Cancer 2011;104:1665-9. Epub April 26, 2011.

BACKGROUND

Gestational trophoblastic disease (GTD) occurs in 1.5 in 1000 pregnancies in the United Kingdom, with the most common expression being the hydatidiform mole. The malignant form, choriocarcinoma, occurs in 1 in 70,000 pregnancies. In the United Kingdom, all of these patients are cared for in specialized centers. Some patients with GTD have hyperthyroidism because they secrete very large amounts of human chorionic gonadotropin (hCG), which can stimulate the thyrotropin (TSH) receptor and cause hyperthyroidism. The purpose of the present study was to review the thyroid function of patients at the Sheffield Trophoblastic Disease Centre in recent years.

METHODS AND RESULTS

During the 5-year period ending January 2010, a total of 196 patients with GTD were treated with

chemotherapy at this center. Only 14 (7%) were found to have biochemical hyperthyroidism, and 4 of these patients had clinical hyperthyroidism. Three of the 4 had hCG levels in excess of 1000 U/ ml at presentation. These 4 patients are described in detail; 3 had lung metastases and 1 had congestive heart failure. Each was treated with carbimazole and chemotherapy for metastatic choriocarcinoma. Thyroid function normalized as serum hCG levels fell. All of these patients were in remission and euthyroid after chemotherapy.

Clinical

THYROIDOLOGY

CONCLUSIONS

Because concomitant biochemical thyroid disease in patients with GTD is relatively common, it is important to assess their thyroid function. The development of hyperthyroidism is largely influenced by the level of hCG and disease burden, and it usually improves with treatment of the persistent GTD. However, in rare cases, the hyperthyroidism can have potentially lifethreatening consequences.

COMMENTARY • • • • • • • • • • • • • • • • •

Because of the common use of ultrasound for following pregnancy, hydatidiform moles are now detected much earlier, when the tumors are smaller and hCG concentrations are not so dramatically elevated. Nevertheless, individual cases of molar pregnancy with hyperthyroidism continue to be reported (1). Centers that specialize in chemotherapy for choriocarcinoma accumulate significant numbers of cases of this rare entity; in the current report, only 4 of 196 (2%) of the patients had significant clinical hyperthyroidism. As has been described in other reports, successful chemotherapy reduces serum hCG levels and cures the hyperthyroidism (2). There are abundant data showing that hCG is a weak thyroid stimulator and binds to the TSH receptor (summarized in reference 3). There are data that indicate that the hCG secreted in GTD is more potent as a TSH than hCG secreted in normal pregnancy (4). This may be attributed to altered glycosylation of the molecule; hCG extracted from hydatidiform moles has reduced sialic acid content and is a more potent thyroid stimulator than normal hCG (5).

- Jerome M. Hershman, MD

HYPERTHYROIDISM DUE TO HCG OCCURS IN 2% OF CASES OF GESTATIONAL TROPHOBLASTIC DISEASE

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Clinical THYROIDOLOGY

A PET/CT THAT IS NEGATIVE MAY BE A COST-EFFECTIVE MODALITY TO AVOID UNNECESSARY SURGERY FOR NODULES WITH NONDIAGNOSTIC CYTOLOGY

Giovanella L, Suriano S, Maffioli M, Ceriani L. ¹⁸FDG-positron emission tomography/computed tomography (PET/CT) scanning in thyroid nodules with nondiagnostic cytology. Clin Endocrinol 2011;74:644-8.

BACKGROUND

Many patients with thyroid nodule fine-needle aspiration (FNA) cytology that is classified as nondiagnostic are put through surgery despite having a benign nodule. This article examines the role of ¹⁸F-fluorodeoxyglucose-positron-emission tomography/computed tomography (¹⁸F-FDG-PET/CT) as a tool to determine whether the nodule can be classified as benign despite the nondiagnostic cytology. It should be noted that the nondiagnostic category is not the indeterminate category. Nondiagnostic usually implies insufficient material for diagnosis and is reported in 5% to 20% of FNA biopsies.

METHODS

In this study, 1648 patients with normal thyrotropin (TSH) levels and a single thyroid nodule >10 mm with suspicious ultrasound characteristics (hypoechoic nodule, >10 mm, irregular margins, chaotic intranodular vascular spots, a shape that was round or more tall than wide, microcalcifications) underwent ultrasound-guided FNA between January 2006 and June 2010. Patients had ¹⁸F-FDG–PET/CT after a 6-hour fast. Any visually discernible ¹⁸FDG uptake within the thyroid nodule (above thyroid tissue background) was classified as positive.

RESULTS

A total of 151 of the 1648 patients (9.2%) had nondiagnostic results and FNA was repeated. Of

these 151 patients, 88 (58%) had results that were still nondiagnostic and were enrolled in the study (61 women, 27 men; mean [±SD] age, 43.5±11.7 years; range, 18 to 79). All 88 patents had ¹⁸F-FDG-PET/CT before they were sent for surgery, and all 88 underwent lobectomy. Histologic analysis of the surgical specimen showed 29 patients (33%) with malignant lesions and 59 (67%) with benign lesions.

Twenty-nine patients with thyroid malignancies had a positive ¹⁸F-FDG–PET/CT scan with focal ¹⁸FDG uptake within the nodule. Among 59 patients with histologically proven benign nodules, 35 displayed no uptake, 16 displayed focal uptake, and 8 (all affected by autoimmune thyroiditis) displayed diffuse or diffuse plus focal uptake.

The sensitivity of ¹⁸F-FDG–PET/CT was 100%, the specificity 69%, the accuracy 79%, the positive predictive value 62%, and the negative predictive value 100%.

CONCLUSIONS

A negative ¹⁸F-FDG-PET/CT scan rules out malignancies among thyroid nodules with nondiagnostic cytology and can serve as a basis to avoid surgical excision. Surgery is still necessary to distinguish benign from malignant disease in nodules that are FDG-positive. Unnecessary surgery could have been reduced from 88 to 41 patients (46%) in this study.

COMMENTARY • • • • • • • • • • • • • • • • •

¹⁸F-FDG–PET/CT is mainly used in the evaluation of patients with metastatic cancer. The role of ¹⁸F-FDG–PET/CT in the treatment of thyroid cancer is limited, and it is used primarily in the postoperative surveillance of patients with differentiated thyroid cancer with positive thyroglobulin and negative radioiodine scans (1). Other indications are initial staging and follow-up of high-risk patients with poorly differentiated thyroid cancer with negative

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A PET/CT THAT IS NEGATIVE MAY BE A COST-EFFECTIVE MODALITY TO AVOID UNNECESSARY SURGERY FOR NODULES WITH NONDIAGNOSTIC CYTOLOGY

radioiodine scans (2). ¹⁸F-FDG–PET/CT also is useful, though somewhat limited, in the evaluation of thyroid nodules with suspicious features on ultrasound.

The ATA guidelines state that patients with nondiagnostic FNA should get a second FNA that is ultrasound-guided (2). The second FNA should be performed 3 months after the initial test (3). If the nodule is partially cystic with some suspicious characteristics, one may elect to follow the patient closely or recommend surgical excision, whereas a solid nodule should be more strongly considered for surgical evaluation after two nondiagnostic FNAs (2, 3). FNA is nondiagnostic in 5% to 20% of cases (4) and repeat FNA under ultrasound guidance may provide a diagnostic specimen in 75% of solid nodules and 50% of cystic nodules (5). A third ultrasound-guided FNA is less likely to be diagnostic. Because only 6% to 20% of patients who have thyroid nodules with nondiagnostic FNA results have thyroid cancer (6, 7), the vast majority of the patients are subjected to unnecessary surgery to rule out malignancy. Negative results on ¹⁸F-FDG-PET/CT may be a cost-effective way to avoid unnecessary surgery.

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Clinical THYROIDOLOGY

LASER PHOTOCOAGULATION OF BENIGN THYROID NODULES IS NOT FIRST-LINE THERAPY IN MOST PATIENTS

Døssing H, Bennedbæk, FN, Hegedüs, L. Long-term outcome following interstitial laser photocoagulation of benign cold thyroid nodules. Eur J Endocrinol 2011;165:123-8. Epub May 6, 2011.

BACKGROUND

Benign nodular thyroid disease is very common in adults. Approximately 20% to 30% of patients who undergo needle biopsy of a solitary nodule will have thyroid surgery for the treatment of thyroid carcinoma or for the diagnosis of cytologically indeterminate or suspicious lesions (1,2). The remaining 70% to 80% of patients with a solitary thyroid nodule are usually treated nonsurgically. If the nodule is especially large, growing, or associated with compressive symptoms, then thyroid surgery is the standard treatment (3), but there are alternative therapies, including percutaneous alcohol ablation, radiofrequency and interstitial laser photocoagulation (ILP). The purpose of this study is to evaluate the long-term efficacy of ILP treatment to reduce the volume of benign thyroid nodules.

METHODS AND RESULTS

During the 9-year period ending in 2008, 78 euthyroid patients with a solitary, solid, scintigraphically cold and cytologically benign nodule were treated with ILP therapy. All patients reported local obstructive symptoms or had cosmetic concerns. All patients had normal thyrotropin (TSH) levels, from 0.3 to 4.0 mU/ ml and a negative basal calcitonin level. Using a 12-MHz linear ultrasound probe with a needle guide, a laser fiber 0.4 mm in diameter was guided into the thyroid nodule through the lumen of an 18-gauge needle. After the needle tip was confirmed to be within the nodule, the needle was withdrawn 2 cm, leaving the end of the laser fiber in direct contact with the tissue. During laser treatment with an output power from 1.5 to 3.5 W using a continuouswave infrared (820 nm) diode laser, necrosis of the tissue was visible as an irregular echogenic area that increased in volume over the treatment time. When the echogenic area stopped increasing in size, the laser fiber was placed in another part of the nodule; this was repeated until all the accessible parts of the nodule were treated.

Using ultrasonography, the nodule volume was calculated before and after the treatment. The overall median nodule volume decreased from 8.2 ml (range, 2 to 25.9) before treatment to 3.5 ml (range, 0.6 to 17.6) after 12 months (P<0.001) and 4.1 ml (range, 0.6 to 33) at the end of the study (P = 0.001). There was a median reduction in nodule volume of 51% (-195%) to 95%). The median treatment duration of the ILP was 900 seconds (range, 292 to 2400), with an overall median energy deposited of 2100 J (range, 438 to 7200), corresponding to 242 J/ml of nodule (range, 21 to 960). There was no significant correlation between thermal energy deposited per nodule volume or the treatment time and the reduction in nodule volume. Using regression analysis, the initial size of the nodule could not predict a successful outcome, but there was a trend for a larger fractional reduction in the size of the nodules that were initially <10 ml. Six of the 78 patients had thyroid surgery 6 months after ILP and 3 patients were lost to follow-up. The mean length of follow-up for the remaining 69 patients was 67 months (range, 12 to 114). An additional 21 patients had thyroid surgery at 12 to 24 months because of an unsatisfactory response. Thus, 27 of 75 patients (36%) required surgery despite having undergone ILP. Initially, 74 patients had pressure symptoms; 84% resolved after ILP. A total of 46 patients had cosmetic symptoms that eventually disappeared in 72%. Both the pressure symptoms and the cosmetic symptoms corrected with nodule-volume reduction after ILP. The serum TSH and antithyroid peroxidase antibody levels did not change during follow-up. The only side effect was moderate pain in 33% of patients that lasted up to 4 days and was alleviated with mild analgesics. None of the patients had vocal-cord palsy, hypocalcemia, hypothyroidism, local infection, or hematoma. The treatment was well tolerated, and all but 1 patient said they would undergo another ILP treatment if offered.

LASER PHOTOCOAGULATION OF BENIGN THYROID NODULES IS NOT FIRST-LINE THERAPY IN MOST PATIENTS

CONCLUSIONS

Ultrasound-guided ILP results in good reduction in pressure symptoms in 84% of patients and reduction of cosmetic symptoms in 72% with a benign solitary solid, cold thyroid nodule. The median reduction in

nodule volume was 51% and was best in nodules <10 ml in size. Thyroid function remained normal, and no complications occurred as a result of the treatment other than moderate pain for up to 4 days.

COMMENTARY • • • • • • • • • • • • • • • • •

Ultrasound-guided ILP results in apparently good reduction in pressure symptoms and volume of benign solitary solid, cold thyroid nodules. The reduction in size was not predictable, and ultimately 36% of patients required thyroidectomy despite having undergone ILP because of an unsatisfactory response. The median reduction in nodule volume was 51%, but the median treatment time was 15 minutes and could last up to 40 minutes with local anesthesia without sedation. This is a very long time for the clinician and for the patient in a busy clinic.

This therapy seems somewhat unpredictable, as the volume reduction was not associated with the time of therapy, the joules delivered, or the size of the nodule. Finally, the therapy worked best for smaller nodules that medically are not usually necessary to remove. The specialized, expensive laser equipment, time to treat, and use of an 18-gauge needle will limit this treatment to specialized centers. It might be considered in patients who are medically unstable for surgery or who refuse surgery.

- Stephanie L. Lee, MD, PhD

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AFTER IODINE-131 THERAPY FOR DIFFERENTIATED THYROID CANCER, INFERTILITY IS LOW AND OBSTETRICAL AND NEONATAL OUTCOMES ARE VERY GOOD

Sioka C, Fotopoulos A. Effects of I-131 therapy on gonads and pregnancy outcome in patients with thyroid cancer. Fertil Steril 2011;95:1552–9.

BACKGROUND

Although radioactive iodine (¹³¹I) therapy is usually well tolerated, side effects that impact future pregnancies can occur such as transient or chronic hypospermia, early onset of menopause, and menstrual cycle abnormalities. The authors reviewed all of the published reports concerning the effects of 131I therapy on female and male gonads and on pregnancy and offspring.

METHODS

Publications related to ¹³¹I effects were identified using PubMed and Medline. Among the abstracts reviewed, 146 full-text articles related to side effects of ¹³¹I were selected, and eventually 54 were used. The criteria used for final selection were the report of the effects of ¹³¹I therapy for thyroid cancer on female and male gonads, lactation, or pregnancy outcome. The review was divided into sections according to the effects of ¹³¹I on female or male gonads, lactation, and pregnancy outcome.

RESULTS

¹³¹I and Ovarian Function

The authors systematically analyzed 16 articles that included data from 3023 women of child-bearing age who had differentiated thyroid cancer (DTC), examining the gonadal and reproductive effects of radioactive iodine therapy. Transient absence of menstrual periods occurred in 8% to 27% of women within the first year after radioactive iodine therapy, particularly in older women. In addition, the ¹³¹I-treated women experienced menopause at a slightly younger age than women not treated with radioactive iodine. Although administration of 3.7 GBq of ¹³¹I may still cause earlier menopause, doses over 3.7 GBq were more likely to increase such a risk. Overall, most studies have demonstrated that, apart from a possible slightly earlier menopausal age, postsurgical administration of ¹³¹I for ablation

of residual thyroid cancer remnants (up to 3.7 GBq activity) resulted in only transient menstrual cycle abnormalities, lasting up to a year, but no permanent ovarian failure. However, repeated doses for recurrent or persistent disease may slightly increase the risk for permanent ovarian failure.

Clinical

THYROIDOLOGY

¹³¹I and Testicular Function

Significant irradiation is delivered to the testes after administration of a single ablative dose to patients who have undergone thyroidectomy. The authors reviewed 8 studies with a total of 306 men of reproductive age receiving doses of ¹³¹I ranging from 1.1 GBq up to 9.2 GBq, with 1 study repeatedly using doses over 22.2 GBq. In most, but not all studies, serum follicle-stimulating hormone (FSH) levels increased between 2 and 6 months after therapy; they very seldom remained elevated by 18 months after therapy. Spermatogenesis was reduced for up to 18 months in all but one study, but permanent impairment was reported only with repeated doses of ¹³¹I. These changes could be significant in subjects with preexisting impairment of fertility.

¹³¹I and Pregnancy Outcome

Eight articles reported the obstetrical outcomes of women treated for DTC. The number of deliveries varied from 49 to 2673. In the largest study (2673 pregnancies), miscarriages rates of 10% before any treatment, 20% after surgery only, and 19% after ¹³¹I treatment were reported. Miscarriages were not significantly more frequent in women treated with radioiodine during the year before conception, not even in women who had received >370 MBq during that year. The incidences of stillbirths, preterm births, low birth weight, congenital malformations, and death during the first year of life were not significantly different before and after ¹³¹I therapy. The incidences of thyroid and nonthyroidal cancers were similar in children born either before or after the mother's exposure to radioiodine. Overall, the studies showed continued on next page

AFTER IODINE-131 THERAPY FOR DIFFERENTIATED THYROID CANCER, INFERTILITY IS LOW AND OBSTETRICAL AND NEONATAL OUTCOMES ARE VERY GOOD

no evidence that exposure to radioiodine affected the outcomes of subsequent pregnancies and offspring.

A comparison of 356 pregnancies from 173 fathers before thyroid cancer diagnosis with 114 pregnancies from 63 fathers with thyroid cancer who received ¹³¹I and with 23 from 17 fathers who had only surgery showed no differences in rates of miscarriage or congenital malformation of offspring before or after the diagnosis of thyroid cancer or after the administration of ¹³¹I.

The above studies provide evidence that previous ¹³¹I therapy in male or female patients did not significantly affect the subsequent pregnancy outcome and did not increase congenital anomalies in the offspring. Avoidance of conception for 6 to 12 months after ¹³¹I therapy is recommended for both male and female patients, to allow for complete replacement of irradiated spermatozoa and reversal of the transient ovarian damage. However, ¹³¹I therapy may still result in a reduced ability to conceive, especially in male patients, in older patients, and in patients treated with multiple doses of ¹³¹I. In such cases, referral to physicians specializing in fertility management may be required.

¹³¹I and Lactation

Reports of the transfer of radioiodine into human milk are rare. Radioiodine uptake is rarely observed in normal breast tissue, but it does occur in the lactating breast. Accumulation of ¹³¹I in the breast may be an undesirable effect of ¹³¹I ablation. Patients should be instructed to avoid both pregnancy and breastfeeding for 6 to 12 months after radiotherapy.

CONCLUSIONS

Transient amenorrhea or menstrual irregularities, which usually resolve within 1 year, can be expected in about 30% of patients who have received therapeutic ¹³¹I. Male patients demonstrate transient impairment of spermatogenesis associated with elevation of FSH, which is reversed within 18 months after ¹³¹I therapy. However, the risk of persistent male or female gonadal dysfunction may be increased in some patients after repeated or high cumulative radioiodine activities. No effects of ¹³¹I on subsequent pregnancy outcomes and on offspring have been documented in either fathers or mothers. Although ¹³¹I therapy is safe overall, most authorities recommend withholding pregnancy until 1 year after ¹³¹I ablation therapy to allow enough time for complete replacement of irradiated spermatozoa and reversal of transient ovarian damage.

One common concerned of women and men who need ¹³¹I ablation therapy after thyroidectomy for DTC is the risk of maternal and neonatal complications in future pregnancies. The other, almost universal, question is the effect of therapy on fertility. The complete review of the literature by Sioka and Fotopoulos, showed a remarkable consistency of results and conclusions among the investigators reporting on the subject. There are very few studies on the effect of ¹³¹I therapy on lactation, but the recommendation is to not offer ¹³¹I therapy to nursing women or that lactation be discontinued 1 to 2 months before ¹³¹I therapy, but the minimal time is several days (1,2). The advice commonly given to women who want to become pregnant is to wait for 6 to 12 months, until remission of thyroid cancer is confirmed. Fairly good studies support this recommendation. Birth control should be strongly advised until the end of this waiting period. Another important basis for recommending a waiting period before becoming pregnant is to achieve the target thyrotropin value. Perhaps something not usually discussed with male patients is the potential effect on fertility, since men with unknown reduced fertility could be exposed to ¹³¹I therapy. It has been suggested that sperm banking should be considered in those requiring cumulative doses of ¹³¹I (3). Finally, the indications for ¹³¹I therapy after thyroidectomy for DTC should be carefully reviewed and the guidelines from the ATA task force should be followed (4).

— Jorge H. Mestman, MD

AFTER IODINE-131 THERAPY FOR DIFFERENTIATED THYROID CANCER, INFERTILITY IS LOW AND OBSTETRICAL AND NEONATAL OUTCOMES ARE VERY GOOD

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ADDISON'S DISEASE IS MORE CLOSELY ASSOCIATED WITH HASHIMOTO'S THAN WITH GRAVES' DISEASE

Wiebolt J, Achterbergh R, den Boer A, van der Leij S, Marsch E, Suelmann B, de Vries R, van Haeften TW. Clustering of additional autoimmunity behaves differently in Hashimoto's patients compared with Graves' patients. Eur J Endocrinol 2011;164:789-94. Epub March 4, 2011.

BACKGROUND

The category of autoimmune thyroid disease (AITD) includes Hashimoto's disease and Graves' disease; these diseases are often part of autoimmune polyglandular syndromes. The purpose of this study was to determine the frequency of adrenal, beta-cell, celiac, and gastric antibodies in patients with AITD and to determine whether there is a difference in the frequency of these antibodies in patients with Hashimoto's as compared with Graves' disease.

METHODS

When patients were diagnosed with AITD and during annual follow-up, antibody studies were performed to determine the presence of other autoimmune diseases—primarily Addison's disease, type 1 diabetes mellitus, celiac disease, atrophic gastritis, pernicious anemia, and vitamin B12 deficiency. When antibody studies were positive, patients underwent clinical evaluation for the presence of the disease. As example, if antiadrenal antibodies were found, patients had an ACTH stimulation test.

RESULTS

There were a total of 882 patients, 523 with Graves'

disease and 359 with Hashimoto's thyroiditis; all were Caucasian. The mean age was about 50 years and the duration of disease about 11 years. Addison's disease was more prevalent in Hashimoto's than in Graves' disease (5.3% and 1.7%, respectively; P<0.03; odds ratio [OR], 3.19). Type 1 diabetes was more prevalent in Hashimoto's disease than in Graves' disease (15.9% and 9.2%, respectively; P<0.03). Beta-ell autoimmunity was also more prevalent in Hashimoto's disease (25.4%) than in Graves' disease (15.6%; P<0.001; OR, 1.84). In patients without type 1 diabetes, the frequency of GAD antibody was similar in Hashimoto's disease and Graves' disease (6.6% vs. 4.6%). There were no significant differences in gastric autoimmunity between Hashimoto's disease and Graves' disease (23.4% vs. 19.2%). The incidence of celiac autoimmunity was 1.2% in both Hashimoto's disease and Graves' disease. In patients with Hashimoto's disease, there was a clustering of gastric autoimmunity with adrenal autoimmunity, and this was not seen in patients with Graves' disease.

CONCLUSIONS

Hashimoto's disease shows a markedly higher clustering of additional autoimmunity, especially with adrenal and beta-cell autoimmunity, as compared with Graves' disease.

COMMENTARY • • • • • • • • • • • • • • • •

I must admit that I have not recommended that patients with Hashimoto's thyroiditis be routinely evaluated for adrenal insufficiency in the absence of clinical features of Addison's disease. At a postgraduate teaching program, my late friend, Clark Sawin, advocated that this be done, and I disagreed with him. The current data showing a 5% incidence of adrenal insufficiency in these patients certainly favor Clark's point of view, even though it does not fit with my experience. A recent study in the United Kingdom reported that the incidence of Addison's disease was 1.4% in Hashimoto's thyroiditis and only 0.11% in Graves' disease (1). Still, it would be undesirable to miss even this 1.4% incidence of Addison's disease in patients with autoimmune thyroiditis. Perhaps adrenal insufficiency will explain some of the lack of well-being in patients with hypothyroidism who are treated with levothyroxine to restore a normal serum thyrotropin. I shall now be more alert to this possibility.

— Jerome M. Hershman, MD continued on next page

Clinical THYROIDOLOGY

ADDISON'S DISEASE IS MORE CLOSELY ASSOCIATED WITH HASHIMOTO'S THAN WITH GRAVES' DISEASE

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INCREASED DIETARY INTAKE OF NITRATE MAY CAUSE THYROID CANCER IN MEN

Kilfoy BA, Zhang Y, Park Y, Holford TR, Schatzkin A, Hollenbeck A, Ward MH. **Dietary nitrate** and nitrite and the risk of thyroid cancer in the NIH-AARP Diet and Health Study. Int J Cancer 2011;129:160-72. doi: 10.1002/ijc.25650. Epub November 18, 2010.

BACKGROUND

The incidence of thyroid cancer has been increasing during the past few decades. Ionizing radiation is the only well-established causative factor. The present study considered the possibility that nitrate and nitrite intake could play a role, based on the fact that nitrate competitively inhibits iodide transport into the thyroid gland. Also, nitrate is reduced to nitrite by oral bacteria, and nitrite reacts with amines and amides in vivo to form nitrosamines and nitrosamides that are potent carcinogens for animals.

METHODS

The authors used a database of the NIH-AARP Diet and Health Study that was initiated in 1995–1996 when an extensive baseline questionnaire was mailed to 3.5 million AARP members 50 to 71 years of age. A total of 567,169 questionnaires were determined to have been satisfactorily completed. The nitrate and nitrite content of over 3000 foods was determined by review of the literature. Based on a food-frequency questionnaire, the nitrate and nitrite intake of each person was calculated. The major contributors to nitrate intake were lettuce, spinach, and broccoli, and the major contributors to nitrite intake were cold cuts, pasta, and bread. A total of 370 cases of thyroid cancer were identified in this population during a 7-year span, 200 in women and 170 in men; 70% were papillary cancers.

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RESULTS

The incidence of thyroid cancer was 17 in 100,000 patient-years. The mean dietary nitrate intake was 88 mg/day and the mean nitrite intake was 1.2 mg/day. Among men in the highest quintile of nitrate intake, there was a 2.3-fold increased risk of thyroid cancer (95% confidence interval [CI], 1.3 to 4.0). There was a 3-fold increased risk of follicular thyroid cancer in men in the highest quartile of nitrate intake, but this was not found in women. Nitrite intake was associated with an increased trend for follicular thyroid cancer in men but not in women. A borderline significant interaction was found for smoking status and nitrite intake in women with a nonsignificant trend for thyroid cancer in the highest quintile of nitrate and nitrite intake.

CONCLUSIONS

Among men, increasing nitrate intake was positively associated with thyroid cancer, with a relative risk of 2.3 for the highest quintile versus the lowest (95% CI, 1.3 to 4.0), but there was no significant trend with intake among women. Nitrite intake was not associated with risk of thyroid cancer for either men or women.

COMMENTARY • • • • • • • • • • • • • • • • •

Studies to explain the increasing incidence of thyroid cancer are worthwhile. The hypothesis tested by this study is based on the finding that nitrate competitively inhibits iodide uptake by the thyroid. Furthermore, reduced iodide uptake causes increased thyrotropin stimulation, and this could promote thyroid carcinogenesis. Studies with cultured cells that contained the sodium-iodide symporter showed that nitrate has about one eighth the affinity of iodide for the symporter (1). Although thiocyanate generated from smoking was thought to be the main anionic inhibitor of iodide uptake (1), nitrate could also play a significant role. Because the main source of dietary nitrate is leafy vegetables, it is possible that pesticides used in agriculture may be responsible for promoting thyroid cancer.

INCREASED DIETARY INTAKE OF NITRATE MAY CAUSE THYROID CANCER IN MEN

The finding that higher nitrate intake increases the risk for thyroid cancer in men but not in women requires explanation. The same group found a significant association of nitrate intake with thyroid cancer in older women in Iowa (2) and could not offer an explanation for not corroborating this finding in the present larger study. I agree with the conclusion that the role of nitrate in thyroid carcinogenesis is worthy of further study.

— Jerome M. Hershman, MD

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THYROID HORMONE TRANSPORTERS ARE EXPRESSED IN THE HUMAN HYPOTHALAMUS

Alkemade A, Friesema EC, Kalsbeek A, Swaab DF, Visser TJ, Fliers E. **Expression of thyroid hormone transporters in the human hypothalamus.** J Clin Endocrinol Metab 2011;96: E967-71. Epub April 20, 2011.

SUMMARY • • • • • • • • • • • • • • • • • •

BACKGROUND

Three revolutions have markedly advanced our knowledge of thyroid hormone action: the discovery of deiodinases (DIO) and of nuclear thyroid hormone receptors in the 1970s to 1980s and the detection of plasma membrane transporters in the past 10 years. MCT-8 (monocarboxylate transporter) was the first transporter to be identified. Inactivating mutations of MCT8 result in the severely debilitating Allan-Herndon–Dudley syndrome. This transporter is mainly responsible for neuronal influx of triiodothyronine (T_3) with dramatic consequences when it fails in the function of the human brain. Meanwhile two other transporters, the MCT10 and the OATP1C1 (organic anion transporting polypeptide 1C1) have been identified in humans, the former being relevant for neuronal efflux of thyroid hormones, the latter being mainly a thyroxine (T_4) transporter. Since their function in the central nervous system (CNS) is essential, it is important to localize them in the human hypothalamus. MCT8 has been identified earlier in the neurons and glial cells of the human hypothalamus. The present work extends these findings by convincingly demonstrating that not only MCT8 but also MCT10 and OATP1C1 are expressed in the hypothalamus.

METHODS AND RESULTS

Postmortem hypothalamus specimens from 10 euthyroid subjects and 1 hyperthyroid subject were investigated by immunocytochemical staining. For the OATP1C1 transporter, the adequacy of the antisera was carefully tested in transfected COS cells functionally expressing the transporter.

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OATP1C1 was present in the paraventricular nucleus (PVN), supraoptic nucleus, and infundibular nucleus and in tanocytes along the third ventricle. The signal for MCT8 was restricted to nuclei, but the OATP1C1 signal was also found scattered throughout the hypothalamus in glial cells, particularly along the wall of the third ventricle. MCT10 was equally present in these nuclei and also in other hypothalamic nuclei (for details see Figure 2 of the article). Interestingly, there was no correlation with the corresponding thyroid hormone concentrations either in the euthyroid subjects or in the hyperthyroid subject. It is conceivable that the conclusions.

CONCLUSIONS

The studies show that the T_4 transporter OATP1C1 is ubiquitously present in the glial cells of the hypothalamus, thus supporting the assumption that this transporter allows entry of T_4 into deiodinase type 2 (DIO2)-rich cells. The resulting T_3 is then further transported by MCT8 into neurons. The neurons of the PVN also stain for OATP1C1 and can therefore import T_4 . Since these cells in humans do not contain DIO2, the function of this transporter in these cells is not clear. MCT10, which enhances the export of thyroid hormones, may be implicated together with the T_3 - and T_4 -deiodinating DIO3—in the reduction of thyroid hormone action.

THYROID HORMONE TRANSPORTERS ARE EXPRESSED IN THE HUMAN HYPOTHALAMUS

COMMENTARY • • • • • • • • • • • • • • • • •

Receptors, deiodinases, and membrane transporters are critically linked to each other (1). The study of their colocalization in hypothalamic structures helps us to understand central thyroid hormone action. As an example, colocalization of DIO2 and OATP1C1 in glial cells preserves T_3 production in the PVN in MCT8 mutant mice, which may explain the absence of a neurologic phenotype in mice.

Meanwhile, TSH, free T_4 and free T_3 levels are still the only clinical tools for evaluating peripheral thyroid

hormone action. By reading about the remarkable progress of thyroid hormone transport, clinicians will realize that our clinical judgment is only a crude appreciation of thyroid hormone function at the level of the target cell. Indeed, it may be quite different in the CNS and pituitary in comparison with the periphery. Perhaps, because of the new insights into the function of thyroid hormone transporters and action we will be able to give more refined answers to many clinically relevant questions.

- Albert G. Burger, MD

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WHY DID TSH RECEPTOR MUTATIONS THAT CAUSED FRANK HYPOTHYROIDISM IN A PATIENT CAUSE ONLY SUBCLINICAL TSH RESISTANCE IN HER SIBLING?

Narumi S, Nagasaki K, Ishii T, Muroya K, Asakura Y, Adachi M, Hasegawa T. **Nonclassic TSH Resistance: TSHR Mutation Carriers with Discrepantly High Thyroidal Iodine Uptake.** J Clin Endocrinol Metab. June 15, 2011 [Epub ahead of print]. doi:10.1210/jc.2011-0070.

SUMMARY • • • • • • • • • • • • • • • • • •

BACKGROUND

If a high thyrotropin (TSH) level is found on screening a newborn infant, but neither a goiter nor thyroid agenesis/dysgenesis is present, about 15% of the time it will turn out to reflect a genetic defect in hormone production. Some patients with mutations in the TSH receptor (TSHR) display frank hypothyroidism, yet the same mutations cause only subclinical/ compensated TSH resistance in other patients; such variable penetrance remains poorly understood. In Japan, the commonest TSHR mutation occurs in the first intracellular loop (ICL1), where a mutation at codon 450 substitutes histidine for arginine (R450H). About 1 in 300 Japanese carry this mutation, but many who carry it are not detected by newborn screening.

ICL1 is one of the regions in the TSHR that interact with the Gq heterotrimer. Gq activates pathways that promote production of H_2O_2 , which is necessary for making thyroid hormone. The level of TSH required to activate the Gq path is much higher than is required to activate the Gs path, which uses cAMP to increase sodium–iodide symporter (NIS) activity and to release thyroid hormone.

METHODS

Patients previously diagnosed with congenital hypothyroidism were reevaluated years to decades later. After briefly discontinuing levothyroxine (L-T₄), their 24-hour uptake of radioactive iodine (123 I) was measured. Of more than 100 patients tested, 24 were found to have a 123 I uptake exceeding 40%. The TSH receptor alleles in those patients were sequenced.

RESULTS

A 15-year-old girl was found to have the R450H mutation on one allele and a T145I mutation on the other. She had no goiter, and after stopping her $L-T_4$ dose, the free thyroxine (T₄) was 0.6 ng/dl, the TSH

53.8 mU/L, the ¹²³I uptake 43%, and the perchlorate discharge test negative. The patient's 13-year-old brother had the same two mutant alleles but was clinically normal, and he had normal thyroid hormone levels and a normal ¹²³I uptake (18.5%), although his TSH was mildly elevated, at 17.7 mU/L. The gene sequences of thyroglobulin, thyroperoxidase, DUOX2 and DUOXA2, iodotyrosine deiodinase, and pendrin were normal in both siblings (expression of these proteins was not assessed). The two different TSHR mutants were then expressed separately in cultured cells. Coexpression of a reporter for assessing cAMP signaling indicated that this pathway was moderately reduced in cells expressing either mutant, as compared with the response of the normal TSHR. A reporter for assessing Gq signaling indicated that this pathway was moderately reduced in the T145I mutant, but Gq signaling was virtually absent in cells expressing the R450H mutant. These in vitro studies indicate that the predominant defect in the function of the TSHR was its coupling to the Gq pathway.

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CONCLUSIONS

The elevated ¹²³I uptake in this 15-year-old girl is believed to reflect enhanced coupling of the TSHR to Gs in response to her elevated TSH level, which is in compensation for the deficit in TSHR coupling to Gq, although there was also some decrease in coupling to Gs. The authors cite the prior report of a family in which three members had subclinical congenital hypothyroidism and who had high 2-hour ¹²³I uptakes. The three patients were found to be homozygous for a mutation in the third extracellular loop of the TSHR (1). When that mutant was expressed in cultured cells, TSH produced a maximal cAMP response equal to that of cells expressing the normal TSHR. However, Gq signaling — assessed by direct measurement of phosphoinositides — was substantially reduced. Heterozygotes in that family had normal TSH levels and ¹²³I uptake.

WHY DID TSH RECEPTOR MUTATIONS THAT CAUSED FRANK HYPOTHYROIDISM IN A PATIENT CAUSE ONLY SUBCLINICAL TSH RESISTANCE IN HER SIBLING?

COMMENTARY • • • • • • • • • • • • • • • • •

Defective Gq coupling should impair the generation of H₂O₂, and the increased level of TSH would be expected to increase sodium/iodide symporter activity, among other things. Some impairment in organification might have been expected, although the perchlorate discharge test was negative in the girl. However, her brother—who has the same compound heterogeneous mutations—had a normal ¹²³I uptake. The difference in sex between siblings could be an issue, although no sex difference in the ¹²³I uptake has been noted in R450H homozygotes (1,2). Indeed the thyroid defect in homozygotes does not appear very different from what is reported in heterozygotes, other than perhaps a slightly higher dose of L-T₄ being required in some cases (1). In addition, a recent Korean study used technetium-99m-pertechnetate (^{99m}TcO₄) uptake measurements before treatment to categorize 193 neonates with permanent congenital hypothyroidism. Of 79 whose ^{99m}TcO₄ uptake was less than 2.5%, 13 were found to have TSHR mutations,

7 being the R450H mutation. In contrast, of 114 whose uptake was greater than 2.5%, only one had R450H, and of the 68 whose uptake was greater than 7%, none had R450H (2). However, there is a recent wrinkle to the Gq story: it now seems that before the TSH receptor can couple with Gq, the TSHR must be dimerized, and then two molecules of TSH must bind to the dimer (3). This raises the issue of how well a mutant TSHR allele can dimerize with the normal TSHR and also with itself.

Whatever the underlying cause, a recent Greek study reported that over 70% of 3- to 5-day-old infants whose TSH is between 10 and 20 mU/L will turn out to have permanent hypothyroidism when reassessed at 3 years (4). This supports the belief that newborns with mild TSH elevations who have a mutation in their TSH receptor probably should be given L-T₄ replacement, even if their thyroid hormone levels are normal (1).

- Stephen W. Spaulding

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Target Audience (Who Should Attend): ATA webinars are designed for endocrinologists, internists, surgeons, basic scientists, nuclear medicine scientists, pathologists, endocrine and surgery fellows, nurses, physician assistants and other health care professionals who wish to broaden and update their knowledge of the thyroid gland and its disorders including clinical management guidelines and recent advances in thyroidology.

Learning Objectives: At the conclusion of ATA webinars, attendees should be able to:

- Describe state-of-the art findings on the mechanisms, prevention, diagnosis, and management of thyroid disorders and cancer
- Explain the latest clinical management guidelines to benefit patient care and the expertise of the clinician in practice
- Describe the impact of health policy, environmental factors, genetic factors, and non-thyroidal conditions on thyroid disorders and cancer
- Explain new treatment options for thyroid disorders and cancer in patient care
- Identify opportunities for increasing education and collaboration to further understand thyroid disorders, thyroid cancer and managing patient care

Disclosures: Disclosures for presenting faculty and content controllers will be provided to attendees verbally or onscreen during the live webinar activity.

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Recorded webinars available for webinars by Drs David Cooper, Michael McDermott, Steven Sherman, Ralph Tufano and William Inabnet at <u>www.thyroid.org</u>

