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A MEK-Inhibitor Enhanced Radioiodine Uptake in Previously Dedifferentiated Thyroid Cancers

Jerome M. Hershman

Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, Pentlow KS, Zanzonico PB, Haque S, Gavane S, Ghossein RA, Ricarte-Filho JC, Domínguez JM, Shen R, Tuttle RM, Larson SM, Fagin JA. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med 2013;368:623-32. doi: 10.1056/NEJMoa1209288.

SUMMARY

Background

Radioiodine-131 has been a mainstay of treatment for differentiated thyroid carcinoma (DTC) for over 50 years. Unfortunately, in many patients with aggressive tumors that recur and metastasize, dedifferentiation occurs and there is loss of iodine uptake by the cancer cells. In such patients, radioiodine therapy is futile and their prognosis is poor. In recent years there have been many basic studies to test agents that may cause a reexpression of the sodium–iodide symporter in thyroid cancer cells that lack this expression. Clinical studies have also been performed with agents, such as retinoids, to increase the uptake of radioiodine by thyroid cancers with very low or no uptake, but none of these studies have resulted in clinically meaningful uptake of radioiodine by tumors that did not show uptake beforehand. The current paper shows that this goal of redifferentiation is attainable with use of a mitogen-activated protein kinase kinase (MEK) inhibitor, as had been shown in animal models (1).

Methods

Patients selected for treatment with the MEK inhibitor, selumetinib, had radioiodine-refractory metastatic disease that was positive on PET scanning. The baseline iodine avidity of their lesion was first assessed with a recombinant TSH-stimulated ^{124}I PET-CT scan. Patients were then treated with selumetinib for 4 weeks. In the last week of treatment, a second TSH-stimulated ^{124}I PET-CT study was performed. Patients with ^{124}I dosimetry that predicted

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tumor uptake of less than 2000 cGy were excluded from further study. If the absorbed dose of radioiodine-131 in the lesion was predicted to be ≥2000 cGy, full dosimetry with iodine-131 was performed to calculate the maximum tolerable activity that could be administered safely. The patient then received a therapeutic dose of radioiodine-131 after preparation with recombinant TSH. Selumetinib was continued until 2 days after the therapeutic dose of ^{131}I. Thyroglobulin levels and the imaging response were evaluated at 2 and 6 months after this therapy.

Genotyping for oncogenic mutations was carried out on paraffin-embedded archival samples.

The primary end point was an increase in ^{124}I PET-quantified iodine uptake and the tumor response at 2 and 6 months; the secondary end point was a decrease in the serum Tg level.

Results

Twenty patients completed the study; 5 had classic papillary thyroid cancer, 8 had tall-cell variant papillary thyroid cancer, and 7 had poorly differentiated carcinoma. Nine patients had a BRAF V600E mutation, 5 had an NRAS mutation, 3 had RET/PTC rearrangements, and 3 had no detectable oncogenic mutations.

Twelve patients had increased ^{124}I uptake after selumetinib, and in 8 the uptake showed that the radiation dose in the lesion would be ≥2000 cGy with ≤300 mCi ^{131}I. These 8 patients were treated with ^{131}I. Only 1 of 9 patients with the BRAF mutation had increased ^{124}I uptake, but all 5 with NRAS mutations had increased uptake. Analysis of lesions showed dramatically increased uptake in some lung and bone lesions.

At the 6-month follow-up, there was a reduction in the size of target lesions in all patients. There was a partial response in six patients and stable disease in two others. The TSH-stimulated serum Tg was reduced by 80% at 6 months.

Side effects of selumetinib included fatigue, rash, and mild liver-enzyme abnormalities. One patient with a cumulative 976 mCi ^{131}I dose before the study received another 139 mCi as a result of the study. One year later he had a myelodysplastic syndrome that progressed to acute leukemia.

Conclusions

The MEK inhibitor selumetinib produced clinically meaningful increases in iodine uptake in a subgroup of patients with thyroid cancer that was refractory to radioiodine, resulting in good clinical responses to ^{131}I therapy.

ANALYSIS AND COMMENTARY

This is a very impressive study, the first to show that a drug caused clinically meaningful radioiodine uptake in DTC that had become dedifferentiated before treatment with the drug, in this case, the MEK inhibitor selumetinib. This therapy should be very useful for treatment of lung metastases that no longer concentrate radioiodine and for lesions in other areas that cannot be resected. The quantitation of uptake with ^{124}I-PET scans is not likely to be available in many centers. Nevertheless, confirmatory studies with less rigorous protocols will be necessary before selumetinib can be approved for this purpose.

It is interesting but unfortunate that only 1 of 9 DTCs expressing the BRAF oncogene had a good response to selumetinib because DTCs with this oncogene

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have a poor prognosis (2). On the other hand, all 5 DTCs expressing NRAS responded very well to selumetinib. Because of the small numbers of patients, it is too early to assume that this prediction of response by genotyping oncogenes will hold up with further studies, but additional studies that include genotyping will be helpful.

The side effects of tyrosine kinase inhibitors, such as selumetinib, are substantial. Fortunately, the short duration of therapy limited the severity of the side effects in this study. Therapy for only several weeks should help to make this treatment method acceptable to patients.

References

1. Chakravarty D, Santos E, Ryder M, et al. Small-molecule MAPK inhibitors restore radioiodine incorporation in mouse thyroid cancers with conditional BRAF activation. J Clin Invest 2011;121:4700-11. Epub November 21, 2011.
2. Xing M. BRAF mutation in papillary thyroid cancer: pathogenic role, molecular bases, and clinical implications. Endocr Rev 2007;28:742-62. Epub October 16, 2007.

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Diagnostic ^{131}I SPECT/CT Scans Detect Unsuspected Metastases after Thyroidectomy for DTC

Jerome M. Hershman

Avram AM, Fig LM, Frey KA, Gross MD, Wong KK. Preablation 131-I scans with SPECT/CT in postoperative thyroid cancer patients: what is the impact on staging? J Clin Endocrinol Metab 2013;98:1163-71. Epub February 21, 2013.

SUMMARY

Background

After surgery for differentiated thyroid cancer (DTC), routine post operative radioiodine scans have largely been abandoned for several reasons. First, the use of relatively large doses of radioiodine may "stun" residual thyroid tissue and prevent the uptake of a subsequent therapeutic dose. Second, in young patients with tumors <2 cm and no evidence of metastatic disease, routine thyroid ablation is no longer recommended. Third, in patients who are selected for radioiodine ablation, the posttherapy scan is believed to provide more information because it results from a much larger dose than that used for diagnostic scans. However, there have been advances in scanning technology that have resulted in better-quality diagnostic scans. In the present study, the authors prospectively performed postoperative scans in patients with DTC using single-photon-emission computed tomography (SPECT) combined with inline computed tomography (CT) that provides coregistration of tomographic functional data.

Methods

Between April 2007 and April 2011, all patients with DTC at the University of Michigan who were referred for postoperative ^{131}I therapy underwent preablation ^{131}I planar and SPECT/CT imaging after a 2-week preparation with a low-iodine diet under conditions of thyroid hormone withdrawal. Images were acquired 24 hours after the administration of 1 mCi ^{131}I. Data were analyzed according to TNM staging and age <45 or ≥45 years. The diagnostic scans were evaluated by two experienced nuclear medicine specialists; one was unaware of the clinical data.

Results

Data were acquired on 320 patients; 43% were <45 years of age, and 68% were women. Ninety percent had papillary cancer. Regional nodal metastases were present in 47% of resected specimens.

The two observers agreed on interpretation of the scans in 84% of the cases. In 138 patients <45, the SPECT/CT detected distant metastases in 5 (4%), restaging them to stage 2, and nodal metastases in 61 (44%), of whom 24 were not considered to have nodal metastases at surgery. In 182 patients ≥45, the SPECT/CT detected distant metastases in 18 (10%) and nodal metastases in 51 (28%). Incorporation of these findings led to upstaging of the disease in 25% of the older patients.

In 67 patients with tumors of 1 to 2 cm, nodal metastases were found by SPECT/CT in 35 (52%) and distant metastases in 3 (4.5%). In 49 patients with tumors <1 cm, nodal metastases were found in 11 (22%) and distant metastases in 2 (4%).

In 303 patients, the diagnostic scan results were compared with the posttherapy scans. The results were concordant in 92%. In 6%, additional foci were found on the posttherapy scans, but new metastatic lesions were found in only 1.4%.

Conclusions

Diagnostic preablation SPECT/CT scans detected regional metastases in 35% of patients and distant metastases in 8% of patients. This information changed staging in 4% of younger and 25% of older patients.

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ANALYSIS AND COMMENTARY

This study could dramatically alter the use of diagnostic ^{131}I scans after thyroidectomy in patients who have undergone surgery for DTC. However, there is one major caveat. The group of patients studied were highly selected because they were referred to a nuclear medicine unit for ^{131}I ablation therapy, even though 43% were younger patients and less than one-half had nodal disease. The patients had more aggressive tumors than the usual group of patients with DTC. Pathology showed that 30% had vascular invasion, 63% had capsular invasion, and 26% had positive surgical margins.

The SPEC/CT showed an impressive number of patients with residual nodal disease. The finding of distant metastases on the scans in over one fourth of older patients is very surprising. There was no information provided with regard to how many of these new findings occurred in the patients with more aggressive pathologic results. In addition, there was no information concerning correlation with serum thyroglobulin in this group with distant metastases. Although the scans were read to include the classification of uptake in the thyroid bed, there was no comment on the frequency of this finding.

In patients selected for ^{131}I ablation, the positive findings on diagnostic SPECT/CT could influence the amount of the dose for ablation. Others have claimed utility for diagnostic ^{131}I scans before ablation (1). One study reported that SPECT/CT performed after radioablation was much more sensitive than planar imaging and detected nodal involvement in one fourth of patients with papillary thyroid carcinoma (2).

If the improved sensitivity for finding residual disease by SPECT/CT is confirmed in an unselected group of patients with DCT, then the wheel will have come full circle by returning to routine ^{131}I diagnostic scans in virtually all patients, a practice largely abandoned over a decade ago based on data showing that stimulated thyroglobulin and neck ultrasound are more sensitive diagnostic tools than ^{131}I scans. In the meantime, this study influences me to consider SPECT/CT for patients who are classified as low risk and who are not selected for ^{131}I ablation because a negative result would give the patient a very good prognosis. Of course cost considerations would influence the decision to use SPECT/CT in such a patient.

References

1. Van Nostrand D, Aiken M, Atkins F, Moreau S, Garcia C, Acio E, Burman K, Wartofsky L. The utility of radioiodine scans prior to iodine 131 ablation in patients with well-differentiated thyroid cancer. Thyroid 2009;19:849-55.
2. Mustafa M, Kuwert T, Weber K, Knesewitsch P, Negele T, Haug A, Linke R, Bartenstein P, Schmidt D. Regional lymph node involvement in T1 papillary thyroid carcinoma: a bicentric prospective SPECT/CT study. Eur J Nucl Med Mol Imaging 2010;37:1462-6. Epub April 1, 2010.

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Nonoccult Differentiated Thyroid Cancer Exhibits Aggressive Behavior in Graves' Disease

Jorge H. Mestman

Pellegriti G, Mannarino C, Russo M , Terranova R, Marturano I, Vigneri R, Belfour A. Increased mortality in patients with differentiated thyroid cancer associated with Graves' disease. J Clin Endocrinol Metab 2013;98:1014-21. Epub January 24, 2013.

SUMMARY

Background

Reports in the medical literature with regard to the aggressiveness of differentiated thyroid cancer (DTC) diagnosed in patients with active Graves' hyperthyroidism are controversial. In previous publications, the authors reported that DTC is more aggressive and has a poorer prognosis in patients with Graves' disease (GD) as compared with DTC in euthyroid patients. The authors speculated that genetic and environmental factors, as well as the lack of appropriate control subjects and/or inadequate patient follow-up, could account for these discrepancies. The objective of this study was to investigate the long-term disease-specific mortality of nonoccult DTCs occurring in patients with GD as compared with DTCs in matched euthyroid control patients.

Methods

The authors studied previously described cohorts of nonoccult DTCs occurring in either patients with Graves' hyperthyroidism (DTC-GD, n = 21) or matched euthyroid control patients with DTC who were recruited in the period 1982–1994 at a single institution (n = 70). The patients were evaluated after follow-up ranging from 50 to 364 months (median, 166) to compare the major clinical end points of persistent/recurrent disease and overall survival. All patients had undergone total thyroidectomy and were followed according to a standardized protocol.

Results

Persistent/recurrent disease was more frequent in patients with DTC-GD than in control patients (P = 0.0119). Disease-specific mortality was also significantly higher in patients with DTC-GD (6 of 21, 28.6%) than in euthyroid control patients (2 of 70, 2.9%) (P = 0.0001). At the last visit, the percentage of disease-free patients was 57.1% (12 of 21) in the DTC-GD group versus 87.1% (61 of 70) in the control group (P = 0.0025).

Conclusions

The authors concluded that non-occult DTCs occurring in patients with GD caused increased disease-specific mortality as compared with DTCs in matched euthyroid patients. These findings emphasize the need for early diagnosis and aggressive treatment of nonoccult DTCs in patients with GD

ANALYSIS AND COMMENTARY

The increased risk of mortality in hyperthyroidism is well documented and was recently analyzed by Spaulding in the February issue of Clinical Thyroidology (1). Increased aggressiveness of concomitant DTC in patients with hyperthyroidism should be added to the list of risk factors. In this long-term follow-up study, Pellegriti et al. excluded patients with occult DTCs incidentally found at surgery, because in a previous publication the authors reported good long-term prognosis in patients with occult thyroid tumors (2). Of the 35 DTCs diagnosed among the 550 patients with GD operated on in the period 1982–1994, a total of 14 cases were incidental occult car-

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cinomas. In the present study, 21 nonoccult DTCs were compared with 70 DTCs occurring in matched euthyroid patients. All patients with DTCs included in this study underwent total or near-total thyroidectomy plus central compartment lymph-node dissection. Serum TSH-receptor antibodies (TSHR-Abs), antimicrosomal antibodies, and/or antithyroglobulin antibodies were obtained before surgery.

After 14 years of patient follow-up, the disease-specific mortality in patients with Graves' disease is alarming (6 of 21 [28.6%]) as compared with the euthyroid patients (2 of 27 [2.9%]). At the end of the study, the percentage of disease-free patients was 57.1% in the DTC-GD group versus 87.1% in the control group. There was no statistical difference between the groups in age, sex, the papillary histotype, or tumor size. There was a trend toward a higher frequency of high-stage tumors in the DTC-GD group, but the difference did not reach statistical significance. By applying multivariate Cox analysis, the authors found that only two variables, stage and GD, were significantly and independently associated with relapses and with cancer-specific deaths. In patients with stage III–IV cancer, but not in those with stage I–II cancer, relapses were significantly more frequent ($P = 0.0062$) in patients with GD than in euthyroid control patients.

Circulating TSHR-Abs were present in all patients in whom a recurrence developed, and they persisted as long as signs of disease were evident. Only one patient had a negative titer before surgery. The authors discussed the potential role of TSHR-Abs in thyroid cancer initiation and progression, and the mitogenic and anti-apoptotic effects elicited by both TSH and TSHR-Abs in thyroid follicular cells.

According to the authors, only two other studies have used a control group of euthyroid patients (2, 3). Both these studies did not show a worse outcome of DTCs associated with GD. The authors speculated that the difference between the studies could be due to the inclusion of a large proportion of occult cancers incidentally found at the postsurgical pathology examination and the fact that the authors' study was performed in eastern Sicily, a region including a volcanic area and whose population has a high incidence of thyroid cancer.

This study has important implications for clinicians who care of patients with Graves' disease, among them: (a) performing a careful physical examination to detect the presence of nodules in these patients, and (b) determination of TSHR-Abs before surgery and regularly during postsurgical follow-up.

References

1. Spaulding SW. How important are preexisting comorbidities and genetic proclivities in explaining the increased risk of mortality in hyperthyroidism? Clin Thyroidol 2013;25:37-9.
2. Pellegriti G, Belfiore A, Giuffrida D, Lupo L, Vigneri R. Outcome of differentiated thyroid cancer in Graves' patients. J Clin Endocrinol Metab 1998;83:2805-9.
3. Yano Y, Shibuya H, Kitagawa W, et al. Recent outcome of Graves' disease patients with papillary thyroid cancer. Eur J Endocrinol 2007;157:325-9.
4. Hales IB, McElduff A, Crummer P, et al. Does Graves' disease or thyrotoxicosis affect the prognosis of thyroid cancer. J Clin Endocrinol Metab. 1992;75:886-9.

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Long-Term Surveillance with Serum Thyroglobulin Might Not Be Worthwhile in Patients with Very-Low-Risk Differentiated Thyroid Cancer

Cord Sturgeon

Durante C, Montesano T, Attard M, Torlontano M, Monzani F, Costante G, Meringolo D, Ferdeghini M, Tumino S, Lamartina L, Paciaroni A, Massa M, Giacomelli L, Ronga G, PTC Study Group. Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: is there a role for serum thyroglobulin measurement? J Clin Endocrinol Metab 2012;97;2748-53, Epub June 7, 2012.

SUMMARY

Background

The postthyroidectomy, postablative stimulated serum thyroglobulin (Tg) level is a sensitive measure of disease burden for differentiated thyroid cancer (DTC). After radioiodine remnant ablation (RRA), it is expected that there should be no detectable Tg in patients who have been cured of cancer and remain disease-free. Because RRA is not routinely used for very-low-risk DTC, the authors wished to evaluate the usefulness of serum Tg measurement in patients who have not undergone RRA for low-risk DTC. The goal of this observational study was to determine the temporal trend of serum Tg levels in patients with low-risk DTC who did not undergo RRA.

Methods

In this multicenter retrospective study, Durante et al. examined the records of 290 patients with low-risk DTC who were treated with total or near-total thyroidectomy but were not given RRA; 287 of these patients had tumors smaller than 1 cm. None of the patients were known to have metastatic lymphadenopathy at the time of surgery. They compared this cohort with a group of 495 patients who did receive RRA. All patients were antithyroglobulin-antibody–negative. Unstimulated Tg levels from the final follow-up visit were recorded for each group. The lower limit of detection for Tg for most subjects was 1 ng/ml. A small subset of RRA-negative patients had highly sensitive assays (threshold sensitivity, 0.2 ng/ml) from the same lab using the same method, and from this group, yearly Tg levels were analyzed (n = 78).

Results

In the RRA-negative group the median tumor size was 4 mm, as compared with a median size of 12 mm in the group that underwent RRA. Only one recurrence was detected in the RRA-negative group, and no recurrences were detected in the RRA-positive group (not statistically significant). Serum Tg levels were >1.0 ng/ml in 5% (17 of 290) of the RRA-negative group and 1% (3 of 495) of the RRA-positive group. This difference was statistically significant. The median serum Tg level in the 17 patients in the RRA-negative group was 2.68 ng/ml. TSH was not suppressed in 46% of the RRA-negative group. In the subgroup of patients who had serum Tg measured with a highly sensitive assay, 60% (47 of 78) had undetectable levels (<0.2 ng/ml) at the first postoperative exam. After 5 years of follow-up, 79% of the patients (number not given) had undetectable serum Tg. In 98.7% (77 of 78) of patients the serum Tg either declined or remained stable over time.

Conclusions

The authors state that their goal was to determine whether Tg assays have any value in the follow-up of patients with DTC who do not undergo RRA after

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total thyroidectomy. They argue that it is difficult to interpret the serum Tg level in patients who have not had RRA after thyroidectomy. Furthermore, they state that cervical ultrasound has a higher diagnostic accuracy than serum Tg or 131I scanning. They concluded that because the serum Tg was below 1 ng/ml in 95% of patients who never underwent RRA (even though many patients did not even have a suppressed TSH) and because the serum Tg declined over time, the serum Tg may not be a reliable marker of disease burden in this population. Finally, the authors call for cost-effectiveness studies and other efforts to determine the proper use of serum Tg and cervical ultrasound in the long-term surveillance of patients with low-risk DTC.

ANALYSIS AND COMMENTARY

Recommendation 32 from the 2009 Revised ATA Guidelines states that RAI ablation is not recommended for patients with unifocal cancer <1 cm without other higher-risk features (1). The guidelines acknowledge that the follow-up of patients who have undergone surgery without RRA may be a challenge. In addition, the guidelines state that "Tg levels should be interpreted in light of the pretest probability of clinically significant residual tumor" and that the Tg trend over time should identify the patients with clinically significant recurrent disease.

This paper does a nice job of describing the long-term kinetics of serum Tg in patients with thyroid cancer who have an extremely low risk of recurrence. It is fascinating to see that the serum Tg levels decline over time in the vast majority of patients with low-risk thyroid cancer who did not get RRA. Although the median follow-up time was a respectable 5 to 6 years, there was only one recurrence identified in the 785 cases included in this study (0.13%). Durante et al. concluded that the serum Tg may not be a reliable marker of disease burden in this population because the serum Tg declined over time and it was below 1 ng/ml in 95% of patients who never underwent RRA. The results, however, should be carefully interpreted, as they may apply only to a small subset of patients with ultra-low-risk thyroid cancer. The median tumor size in the RRA-negative group was only 4 mm, and no subject had extrathyroidal extension or positive lymph nodes. No patients had evidence of vascular invasion or aggressive histology. Eighty percent of these cancers were incidentally found microcarcinomas, some as small as 0.5 mm. Finally, TSH values were not given for the RRA-positive cohort, and it is possible that they may have had a greater degree of TSH suppression.

In 2006, similar results were reported by Torlontano et al. (2). In their study 56% of patients with low-risk papillary thyroid microcarcinoma who did not undergo RRA had a stimulated Tg of <1 ng/ml. They compared ultrasound, whole-body radioiodine scanning and stimulated serum Tg and concluded that cervical ultrasound was the most effective screening tool.

Durante et al. state that they conducted this study to determine the role of serum Tg in the follow-up of patients with low-risk PTC who underwent thyroidectomy without RRA. They concluded that Tg might not be a reliable marker of disease burden in this population. It should be acknowledged, however, that it is possible to make a type II error when studying a finite population with an extremely low rate of clinically meaningful recurrence. In order to further test their hypothesis, the authors might have considered increasing the size of their cohorts, or adding a third group to their study composed of patients who underwent a total or near-total thyroidectomy for benign pathology and for whom postoperative TSH and serum Tg levels were followed.

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In conclusion, patients with well-differentiated microcarcinoma that do not have metastatic lymphadenopathy, vascular invasion, positive margins, extrathyroidal extension, or aggressive histology and who have undergone a total thyroidectomy probably have such a low risk of recurrent or persistent disease that it should call into question the intensity or even the necessity of long-term surveillance with ultrasound, serum Tg, and/or radioiodine scans. The authors appropriately call for studies that could identify the most optimal long-term surveillance strategy for these patients.

References

1. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
2. Torlontano M, Crocetti U, Augello G, D'Aloiso L, Bonfitto N, Varraso A, et al. Comparative evaluation of recombinant human thyrotropin-stimulated thyroglobulin levels, 131I whole-body scintigraphy, and neck ultrasonography in the follow-up of patients with papillary thyroid microcarcinoma who have not undergone radioiodine therapy. J Clin Endocrinol Metab 2006;91:60-3. Epub October 11, 2005.

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Primary Thyroid Lymphomas May Have BRAF Mutations That Suggest a Diagnosis of Thyroid Cancer

Jerome M. Hershman

Aggarwal N, Swerdlow SH, Kelly LM, Ogilvie JB, Nikiforova MN, Sathanoori M, Nikiforov YE. Thyroid carcinoma-associated genetic mutations also occur in thyroid lymphomas. Mod Pathol 2012;25:1203-11. Epub May 11, 2012.

SUMMARY

Background

The BRAF V600E oncogenic mutation is found in 40% to 45% of papillary thyroid carcinomas (PTCs). It activates the mitogen-activated protein kinase (MAPK) signaling pathway. Because this mutation can be detected in thyroid FNA aspirates, screening for it has been advocated (1). The BRAF V600E mutation is also found in anaplastic or poorly differentiated thyroid cancers that have a papillary component. Primary thyroid lymphomas are relatively rare and frequently present as rapidly growing masses in the thyroid gland. The present report shows that a significant number of thyroid lymphomas have BRAF mutations, although only the index case in this series had the BRAF V600E mutation.

Methods

Archived pathology specimens of 33 primary thyroid B-cell lymphomas were studied for mutations in the MAPK signaling pathway. Microdissection of the specimens was performed; the DNA was isolated and studied by real-time PCR. The hot spots in BRAF codons were amplified and sequenced. The DNA was also studied for mutations in NRAS, HRAS, and KRAS.

Results

In a patient with a thyroid mass, FNA was used to diagnose both carcinoma and lymphoma. Molecular analysis of the aspirate was positive for the BRAF V600E mutation. After excision, the tumor was found to be a diffuse large-B-cell lymphoma, and there was no PTC in the thyroid. This led to the study of 33 thyroid lymphomas that came from 28 women and 5 men with a mean age of 65 years; 25 were diffuse large-B-cell lymphomas, 6 were extranodal marginal-zone lymphomas, and 2 were follicular lymphomas. Eight of the 33 lymphomas were positive for one of the studied mutations. There were six BRAF mutations, including the BRAF V600E mutation found in the index case, three D594G mutations, and two K601N mutations. In addition, there were 2 NRAS mutations, Q61K and Q61H. All of these mutations were identified in the diffuse large-B-cell lymphomas. None of the cases had mutations in KRAS or HRAS.

The patients were treated with surgery, radiation, and chemotherapy. Eleven of the 33 died from the lymphoma. There was no difference in survival between the group with and that without mutations.

Conclusions

The data show that, when a BRAF or NRAS mutation is found in a thyroid aspirate, the differential diagnosis should include primary thyroid lymphoma in addition to thyroid carcinoma.

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ANALYSIS AND COMMENTARY

The authors state that this is the first report of BRAF and NRAS mutations in primary thyroid lymphomas. Lee et al. reported that 4 of 67 diffuse large-B-cell lymphomas found in nonthyroid sites had BRAF mutations, but they were not in codon 600 (2). At the most recent ATA meeting in Quebec, Jayakumar and Shifrin reported a patient with thyroid lymphoma that had the BRAF V600E mutation (Program of the 82nd Annual Meeting of the American Thyroid Association, page 194). Last year we performed an FNA of a 1.9-cm thyroid nodule in a patient who had been treated 2 years earlier for diffuse large-B-cell lymphoma and was considered disease-free. The aspirate yielded only atypical lymphoid cells and was positive for the BRAF V600E mutation.

The BRAF V600E mutation is found in many cancers besides PTC: about half of cases of metastatic melanoma, a small fraction of colon cancers, and nearly all of hairy-cell leukemias, among others. The NRAS Q61K mutation identified in this study is commonly seen in follicular thyroid cancer (3). As mutation analysis is applied more commonly to thyroid lesions, one must be aware that nonthyroid neoplasms may harbor activating mutations of the MAPK pathway, even when the lesions reside in the thyroid area.

Primary thyroid lymphoma is usually found in patients with a background of Hashimoto's thyroiditis (4). Unfortunately, the current report did not provide data in this regard.

References

1. Nikiforov YE, Ohori NP, Hodak SP, Carty SE, LeBeau SO, Ferris RL, Yip L, Seethala RR, Tublin ME, Stang MT, Coyne C, Johnson JT, Stewart AF, Nikiforova MN. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. J Clin Endocrinol Metab 2011;96:3390-7. Epub August 31, 2011.
2. Lee JW, Yoo NJ, Soung YH, Kim HS, Park WS, Kim SY, Lee JH, Park JY, Cho YG, Kim CJ, Ko YH, Kim SH, Nam SW, Lee JY, Lee SH. BRAF mutations in non-Hodgkin's lymphoma. Br J Cancer 2003;89:1958-60.
3. Hou P, Liu D, Shan Y, Hu S, Studeman K, Condouris S, Wang Y, Trink A, El-Naggar AK, Tallini G, Vasko V, Xing M. Genetic alterations and their relationship in the phosphatidylinositol 3-kinase/Akt pathway in thyroid cancer. Clin Cancer Res 2007;13:1161-70.
4. Matsuzuka F, Miyauchi A, Katayama S, Narabayashi I, Ikeda H, Kuma K, Sugawara M. Clinical aspects of primary thyroid lymphoma: diagnosis and treatment based on our experience of 119 cases. Thyroid 1993;3:93-9.

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Should Guidelines Be Developed to Indicate When Hyperthyroidism or Hypothyroidism Ought to Be Included on a Death Certificate?

Stephen W. Spaulding

Goldacre MJ, Duncan ME. Death rates for acquired hypothyroidism and thyrotoxicosis in English populations (1979–2010): comparison of underlying cause and all certified causes. QJM, 2012;106: 229-235.

SUMMARY

Background

Death certificates contain the single condition judged to be the underlying cause of death, but may include other diseases considered to be contributory causes as well. The authors used a national English mortality database from 1995-2010, and also a smaller Oxford regional database dating back some 30 years, to calculate the annual age-standardized mortality rates for all cases in which hypothyroidism or hyperthyroidism was mentioned, either as the underlying cause or as a contributory cause. The codes and the rules for coding changed several times in the 1980s and coding also changed in 2001, which required a fairly complicated analysis of the results.

Methods

Robust data were obtained from the English national mortality database, which used the International Classification of Diseases, 9th Revision (ICD9) disease categories from 1995–2000, then switched to ICD10 categories from 2001 to 2010 (this change split the code for hypothyroidism, and removed the code for postsurgical and post irradiation hypothyroidism, putting them under "E89, Post procedural endocrine and metabolic complications and disorders, not otherwise classified"). The 2001–2010 English national data were also used to determine the 12 commonest "contributing factors" included on the certificates of patients who died of hyperthyroidism or hypothyroidism. The authors also determined the 12 commonest causes of death for all certificates that mentioned hyperthyroidism or hypothyroidism as a contributing factor. The data from the smaller Oxford region database that extended back as far as 1979 needed to be addressed in 4 different groups of years because of changes in codes and coding rules.

Age-standardized death rates were determined using age-specific death rates, in 5-year age groups, from the "European Standard Population." An "average annual percentage change" in mortality rate for all certificates containing any mention of hyper- or hypothyroidism was calculated by fitting regression models to the logarithms of the death rates. The significance of differences found between coding periods was assessed by Chi squared testing.

Results

The age-standardized English national data on certificates with any mention of hypothyroidism averaged over the 1995-2000 period did not differ significantly from that of the 2001-2010 period, whereas the percentage of deaths caused by hypothyroidism as a fraction of total mentions of hypothyroidism was actually higher in 2001-2010 than in the previous 1995-2000 period. Examination of the year-by-year graph of the age-standardized mortality rate confirmed the rise in certificates listing hypothyroidism as the underlying cause from 2001-2010, but - unlike the averaged data – showed that total mentions of hypothyroidism consistently and progressively fell from 1995 to 2000, and then consistently and progressively rose from 2001 to 2010. The Oxford

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regional mortality data were much more variable, but the graph of total mentions of hypothyroidism as well as of hypothyroidism as the cause of death trended downwards over the 1979-1995 period, and thereafter generally followed the national trends.

The percent of deaths caused by hyperthyroidism as a fraction of total mentions of hyperthyroidism did not change, based on the age-standardized English national data, averaged over the 1995–2000 period versus the 2001–2010 period. However the "average annual percentage change" in total mentions of hyperthyroidism did decrease significantly, the greatest decrease being in the age group of 65 to 74 years. Examination of the graph of the year-by-year age-standardized mortality rate revealed that total mentions of hyperthyroidism fell substantially and consistently, but that hyperthyroidism as the underlying cause of death also fell consistently. The graph of the Oxford regional graph showed that the total number of mentions of hyperthyroidism as well as deaths caused by hyperthyroidism fell, albeit erratically, from 1979 to 1995. Since 1995 they generally followed the national trends.

In the patients who died from hypothyroidism, the associated causes listed most commonly were, in descending order, pneumonia, followed by dementia, hypertension, chronic ischemic heart disease, atrial fibrillation and heart failure. In the patients who died from hyperthyroidism, the associated conditions most commonly listed also were pneumonia, followed by atrial fibrillation/flutter, hypertension, chronic ischemic heart disease and heart failure. On those death certificates listing hypothyroidism or hyperthyroidism as a contributing factor, the 6 commonest underlying causes of death were identical and in the same order: chronic ischemic heart disease, followed by stroke, myocardial infarction, COPD, dementia and heart failure.

Conclusions

In the Oxford region, particularly in the 1980s, mortality from both thyroid disorders fell, both when listed as a contributing factor and also when listed as the underlying cause of death. Over the past 15 years, the national data showed mortality from hyperthyroidism continued to fall, both as the underlying cause of death and also as the total number of mentions. Mortality from hypothyroidism listed as the cause of death was actually higher in 2001–2010 than in 1995–2000, which the authors attributed to the change in ICD coding of hypothyroidism as the underlying cause of death.

ANALYSIS AND COMMENTARY

The authors surmised that the decreases in thyroid-related mortality they found were likely due to improvements in the treatment of the thyroid conditions—stating that they were not aware of any evidence that the incidence of these thyroid conditions has declined over time; or that physicians have come to believe that fewer patients are dying from these disorders, but rather that the patients are merely dying with them; or that there was increasing reluctance to list these diseases as a cause of death.

We note that the marked improvement in the TSH assay over the period studied has made it embarrassingly clear that our record of maintaining a patient's TSH within the normal range is often less-than-perfect. When completing a death certificate, it is easy to overlook an earlier thyroid disorder if the thyroid function tests were normal at the time the patient died. True, there is evidence the therapy used to treat certain forms of hyperthyroidism has recently undergone change (1), but shifts in racial/ethnic make-up, dietary iodine levels (2) and

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smoking incidence (3) have been documented in the UK, and newer drugs like amiodarone may also have altered the incidence and/or severity of several causes of hyperthyroidism and/or hypothyroidism. Better assays for TSH and TSH-receptor antibodies were introduced, which have helped physicians recognize and treat more subtle diseases, like silent thyroiditis, and hyper- and hypothyroidism in elderly patients, who often lack classical symptoms. These improved assays have also instigated growing concern about morbidity and mortality in so-called subclinical hyperthyroidism and hypothyroidism. Finally, one should note that patients with autoimmune diatheses underlying Graves' and Hashimoto's disease can suffer later mortality due to "unrelated" autoimmune diseases.

Therefore, it might be more credible to ascribe at least some of the decrease in mortality to advances in the care of common disorders like pneumonia, dementia, hypertension, chronic ischemic heart disease, atrial fibrillation and heart failure. This would seem to be consistent with the authors' finding that total mentions of hyperthyroidism decreased the most in the 65-74 age group, in which these diseases may prove fatal. Disregarding the possible effects of thyroid disorders on pre-existing conditions, it is clear that thyroid disorders also can predispose to new medical conditions. Despite some methodological drawbacks, an increasing number of papers indicate that hyperthyroidism and hypothyroidism are associated with an increased risk of mortality, independent of any medical conditions present before the thyroid disorder was diagnosed (4,5). (The association between thyroid disorders and cardiovascular deaths seems to be more well-recognized, thus far, than deaths from osteoporotic hip fractures).

It is striking that less than 1% of patients with a diagnosis of hyperthyroidism or hypothyroidism have that diagnosis listed on their death certificates. (In the United Kingdom, the 2010 death rate was about 5 per 1000 for women and 7 per 1000 in men. A rough estimate of the annual incidence of primary hypothyroidism in women is about 4 per 1000 per year in surviving women and about 0.6 per 1000 in surviving men. The annual incidence of hyperthyroidism is about 1 per 1000 in women and 0. 15 per 1000 in men). The death certificates, on the other hand, mentioned hypothyroidism in only about 0.02 per 1000 women and 0.01 per 1000 in men , and mentioned hyperthyroidism in only about 0.004 per 1000 women and 0.001 per 1000 in men. Interestingly, the mortality rates for women were only 3 times those for men, although their prevalence in women is closer to 10-to-1. Despite the infrequency with which these disorders were mentioned in death records, a substantial fraction of patients with these thyroid diagnoses can have associated comorbidities, and presumably some die because of them. It is also striking that in the 2001–2010 period, 17% of the death certificates that mentioned hypothyroidism actually gave it as the underlying cause of death, and almost a quarter of all certificates that mentioned hyperthyroidism gave it as the underlying cause of death. This fraction of thyroid disorders as the direct cause of death, rather than as associated causes, seems high. What are the reasons for a physician to attribute a death directly to one of these thyroid conditions? An obvious reason would be deaths connected with thyroid storm/crisis or myxedema coma, but these are rare. Another reason could be fatal complications from treatment for the thyroid disorders (although the appropriate coding probably would fall under complications of surgery or of side effects of drugs or of radioiodine administration, while the thyroid disorder would probably be listed as an associated cause).

Unfortunately, death certificates cannot be used to determine the length of time between when the initial diagnosis of a thyroid disorder was made and the time death occurred, what therapies were given, or any associated laboratory or clinical information. Although concerns about privacy remain, the introduction of universal medical records would make it possible someday to devise guidelines for when

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thyroid disorders should be included on a death certificate as a possible associated cause. Should an associated thyroid disorder be included for all deaths from pneumonia, dementia, hypertension, chronic ischemic heart disease, atrial fibrillation and heart failure? Probably yes, if the death occurred within the first year after the thyroid disorder was diagnosed. But what about a patient who died of chronic ischemic heart disease at age 85 after having been "adequately treated" for hypothyroidism for 30 years? What if the hypothyroidism was due to ^{131}I therapy for Graves' disease: shouldn't hyperthyroidism also be included on the death certificate?

References

1. Turner M, Driver I, Salotti JA, Pearce MS, Cheetham T. Increasing use of radioiodine in young people with thyrotoxicosis in Great Britain. Eur J Endocrinol 2013 e-pub before print September 6, 2012, doi: 10.1530/EJE-12-0542.
2. Vanderpump MPJ. Commentary: Iodine deficiency as a new challenge for industrialized countries: a UK perspective. Int J Epidemiol. 2012;41:601–604.
3. Ikuko F, Funatogawa T, Yano E. Impacts of early smoking initiation: long-term trends of lung cancer mortality and smoking initiation from repeated cross-sectional surveys in Great Britain. BMJ Open 2012;2:e001676. DOI:10.1136/bmjopen-2012-001676.
4. Spaulding SW. How Important Are Preexisting Comorbidities and Genetic Proclivities in Explaining the Increased Risk of Mortality in Hyperthyroidism. 2013. Clin Thyroidol 2013;25:37–39.
5. Thvilum M., Brandt F, Almind D, Christensen K, Hegedüs L., Brix TH. Excess Mortality in Patients Diagnosed With Hypothyroidism: A Nationwide Cohort Study of Singletons and Twins. J Clin Endocrinol Metab 2013. Published online, doi: 10.1210/jc.2012-3375.

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Subclinical Hypothyroidism Is a Frequent Finding in Children and Adolescents With Type 1 Diabetes

Albert G. Burger

Denzer C, Karges B, Näke A, Rosenbauer J, Schober E, Schwab O, Holl R. Subclinical hypothyroidism and dyslipidemia in children and adolescents with type 1 diabetes mellitus. Eur J Endocrinol. February 5, 2013 [Epub ahead of print].

SUMMARY

Background

Subclinical hypothyroidism (SCH), defined by an increased serum TSH along with normal free T_4 and free T_3, is a frequent finding in adults with type 1 and type 2 diabetes. In obese nondiabetic children, SCH is more frequent (>10%) than in normal children (1% to 2%) (1). Studies on the prevalence of SCH in children and adolescents (<25 years old) with type 1 diabetes are scarce (2). This large study adds considerable new knowledge to the subject.

Methods

In 1995, a large surveillance database for children and adolescents with type 1 diabetes was established in Germany and Austria (3). Various data from all patients were collected twice yearly. The data from patients with a serum TSH of more than 5 mU/L but less than 25 mU/L were analyzed. In addition to thyroid tests, a lipid profile was obtained in the same blood sample. If multiple samples from the same patient were available, only the last one was considered. Patients with decompensated diabetes or those taking possibly interfering drugs, particularly lipid-lowering substances, were excluded, as were patients affected by familial hypercholesterolemia. A total of 22,747 patients with type 1 diabetes fulfilled the required criteria.

Results

Of the 22,747 children and adolescents with type 1 diabetes type, 19.2% had either anti-TPO and/or antithyroglobulin antibodies, and 7.2% had SCH (TSH, >5 and <25 mU/L; normal free T_4 and free T_3). Arranging the patient data according to quartiles of rising serum TSH revealed a stepwise increase of total cholesterol and LDL cholesterol levels. These increments were already evident with serum TSH levels between 2 and 4 mU/L. There were also increases, albeit very modest ones, in body-mass index (BMI) and high-density lipoprotein (HDL) cholesterol. Patients with higher serum TSH also had significantly higher total cholesterol and low-density lipoprotein (LDL) cholesterol (serum TSH, <4 mU/L: total cholesterol, 173.3 mg/dl [4.54 mmol/L]; TSH: >5 to <25 mU/L: 178.7 mg/dl [4.63 mmol/L]; LDL, 93.7 mg/dl [2.43 mmol/L] for TSH <4 mU/L vs. 97 mg/dl [2.51 mmol/L] for TSH >5 to 25 mU/L). Although BMI was higher in the group with hypothyroidism, there was no difference in mean height. The prevalence of 7.2% of SCH in this study is clearly higher than in a comparable investigation on young healthy adults in which SCH occurred in approximately 2% of subjects (Figure 3 in National Health and Nutrition Survey [NHANES] III) (4).

Conclusions

In children and adolescents with type 1 diabetes, thyroid antibodies are present in 19.2% and subclinical hypothyroidism is present in 7.2%, a value clearly much higher than in a comparable healthy population. With increased serum TSH, there was a gradual increase of serum total and LDL cholesterol reaching significance in SCH. Yet the increase in lipid levels was modest in view of the rather high serum TSH values. In addition, there was a trend toward increased BMI.

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ANALYSIS AND COMMENTARY

The results are remarkable, since they were obtained from a very large population base of young patients with type 1 diabetes. Compared to similar studies in normal subjects, this group of patients had a highly increased incidence of SCH and even a higher incidence of thyroid antibodies. SCH in adults is associated with an increased lipid profile, and most studies suggest an increased cardiovascular risk. Here the authors prove that in a considerable fraction of even a young population with type 1 diabetes, serum lipids are significantly increased. These novel data are therefore an important addition to our knowledge about the connection of diabetes and thyroid disease. In this respect, young patients are not different from adult patients with type 1 diabetes.

One might wonder why the effects of SCH on the lipid profile are so small. This is particularly puzzling, since the range of SCH was defined by a TSH as high as 4 to 25 mU/L. The authors give no information on how many of these patients had a serum TSH in the lower range, for instance between 4 and 10, or 11 and 15 mU/L, etc. However, one may safely guess that the whole sample of study patients contained only a few individuals with a serum TSH as high as 24 mU/L and still normal thyroid hormone levels. At least in adults, it is unusual to find a patient with a serum TSH of 15 mU/L and still normal thyroid hormone levels, and this is even more unlikely for a TSH of 24 mU/L. I suspect that the large majority of the patients included in this study had serum TSH in the low range defined for SCH. If so, this may explain the small effect of SCH on the lipid profile; still, screening for SCH in young patients with type 1 diabetes seems to be highly advisable.

The study also revealed a high prevalence of euthyroid patients with positive thyroid antibodies. The risk of hypothyroidism cannot be neglected in such patients.

Also, the study does not provide arguments as to the question of whether rigorous treatment with thyroxine may improve the lipid profile. It is hoped that the authors will provide data on these important points in a few years. Based on the evidence from adults, it seems reasonable to treat the patients with SCH described here with T_4, particularly if the serum TSH is repeatedly above 7 to 10 mU/L. Some endocrinologists recommend starting treatment even if serum TSH is above 4 mU/L, but there are not data showing benefit from such a treatment.

References

1. Reinehr T. Thyroid function in the nutritionally obese child and adolescent. Curr Opin Pediatr 2011;23:415-20.
2. Kordonouri O, Klinghammer A, Lang EB, Gruters-Kieslich A, Grabert M, Holl RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. Diabetes Care 2002;25:1346-50.
3. Grabert M, Schweiggert F, Holl RW. A framework for diabetes documentation and quality management in Germany: 10 years of experience with DPV. Comput Methods Programs Biomed 2002;69:115-21.
4. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87:489-99.

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Childhood Obesity and Increased Childhood Weight Gain Are Associated with an Increased Risk for Hypothyroidism and TPO Antibody Positivity in Adulthood

Elizabeth N. Pearce

Ong KK, Kuh D, Pierce M, Franklyn JA; on behalf of the Medical Research Council National Survey of Health Development Scientific Data Collection Teams. Childhood weight gain and thyroid autoimmunity at age 60-64 years: the 1946 British Birth Cohort Study. J Clin Endocrinol Metab. February 22, 2013 [Epub ahead of print].

SUMMARY

Background

In previous observational studies, complex associations between thyroid status and body weight have been described. Hypothyroidism causes modest increases in body weight, but obesity is also associated with increased levels of both TSH and serum T_3, which decrease with subsequent weight loss (1, 2). A recent study demonstrated a higher risk for TPO-antibody positivity in obese as compared with normal-weight adults (3).

Methods

This was a prospective observational cohort study using data from the UK Medical Research National Council Survey of Health and Development. A total of 2547 women and 2815 men were initially included in this cohort, representing a socially stratified sample of all births across the United Kingdom within a single week in 1946. Birth weights were recorded, and height and weight were measured at multiple time points between ages 2 and 64. At ages 60 to 64, a total of 3163 subjects were sent survey that included questions regarding diagnoses of thyroid disease and use of thyroid medications. Self-reported diagnoses of thyroid disease were validated by questionnaires sent to participants' primary care providers. In addition, thyroid-function tests (serum TSH, free T_4, and TPO antibodies) were obtained in 2143 participants at ages 60 to 64. In individuals with abnormal TSH and/or free T_4 values, free T_3 concentrations were also measured. Body-mass index (BMI), weight, and height were converted into standardized scores. Overweight/obesity at age 14 was defined as a BMI in the top decile. Weight gain between 0 and 14 years was adjusted for birth weight and by height gain from ages 2 to 14. Analyses were stratified by sex. Logistic regression was used to determine odds ratios for taking levothyroxine (L-T_4) and for having a thyroid disorder in those with and those without overweight/obesity at age 14 and by childhood weight gain. Cross-sectional associations between BMI and thyroid function at ages 60 to 64 among euthyroid participants were also assessed.

Results

At ages 60 to 64, 10.9% of women and 2.3% of men reported use of L-T_4. TPO antibodies were positive in 11.5% of women and 3.3% of men. Women who reported L-T_4 use had higher BMI and body weight at ages 60 to 64 than women not taking L-T_4 (BMI, 28.9 vs. 27.8; P = 0.04; weight, 75.9 kg vs. 72.8 kg; P = 0.03); this difference was not observed in men. The women taking L-T_4 also had higher body weights at all other time points assessed, starting at age 6. Body weight, but not BMI, was higher in TPO-positive than in TPO-negative women at ages 60 to 64 (75.3 kg vs. 72.4 kg; P = 0.04) as well as at earlier time points; this

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difference was not observed in men. In women, but not in men, greater weight gain between birth and age 14 was associated with an increased likelihood for L-T_4 use and for TPO antibody positivity at ages 60 to 64. The women who had been overweight or obese at age 14 were more likely to have positive TPO antibodies at ages 60 to 64, but were not significantly more likely to use L-T_4. In men, overweight or obesity at age 14 was associated with higher likelihood for L-T_4 use, but not for TPO antibody positivity, at ages 60 to 64. After adjustment for weight at age 14, there were no cross-sectional associations between adult weight or BMI at ages 60 to 64 and either L-T_4 use or TPO antibody positivity. Among the 1712 euthyroid, TPO antibody-negative individuals in the cohort, free T_4 was inversely associated with BMI, but there were no associations between BMI at ages 60 to 64 and serum TSH values.

Conclusions

This study demonstrates that in women, childhood overweight/obesity and more rapid childhood weight gain are associated with an increased risk for hypothyroidism and TPO antibody positivity later in life.

ANALYSIS AND COMMENTARY

An association between higher birth weight and adult hypothyroidism had previously been described in a single small study (4). Conversely, in a birth cohort study of 293 women in Finland, lower birth weight and lower weight in childhood were associated with higher risk for hypothyroidism as an adult (5). It is unclear why the results of the larger study by Ong and colleagues are discordant with the Finnish data. There is no clear mechanism to explain why childhood adiposity should predict thyroid dysfunction or autoimmunity. In addition, it is unclear whether effects of childhood obesity and weight gain on adult thyroid function and thyroid autoimmunity are truly sex-specific or whether there were simply too few cases of thyroid dysfunction in the men in this cohort to see associations.

Strengths of this study include its prospective design, representative study sample, and long length of follow-up. Limitations include the loss to follow-up of 28% of the initial cohort, incomplete questionnaire response rates, lack of interval thyroid antibody or thyroid-function measurements prior to ages 60 to 64, and the use of self-report (although validated in most cases by physician questionnaires) to ascertain L-T_4 use. Information about potential confounders, such as family history of obesity and of thyroid dysfunction, was not ascertained.

Rates of childhood obesity have more than doubled in children and tripled in adolescents in the past 30 years, with more than one third of U.S. children and adolescents considered overweight or obese in 2010 (6). These facts, together with the data of Ong and colleagues, suggest that there may be substantial increases in the incidence of hypothyroidism and thyroid autoimmunity in the United States over the next several decades.

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References

1. Biondi B. Thyroid and obesity: an intriguing relationship. J Clin Endocrinol Metab 2010;95:3614-7.
2. Pearce EN. Thyroid hormone and obesity. Curr Opin Endocrinol Diabetes Obes 2012;19:408-13.
3. Marzullo P, Minocci A, Tagliaferri MA, Guzzaloni G, Di Blasio A, De Medici C, Aimaretti G, Liuzzi A. Investigations of thyroid hormones and antibodies in obesity: leptin levels are associated with thyroid autoimmunity independent of bioanthropometric, hormonal, and weight-related determinants. J Clin Endocrinol Metab 2010;95:3965-72. Epub June 9, 2010.
4. Phillips DI, Barker DJ, Osmond C. Infant feeding, fetal growth and adult thyroid function. Acta Endocrinol (Copenh) 1993;129:134-8.
5. Kajantie E, Phillips DI, Osmond C, Barker DJ, Forsén T, Eriksson JG. Spontaneous hypothyroidism in adult women is predicted by small body size at birth and during childhood. J Clin Endocrinol Metab 2006;91:4953-6. Epub September 19, 2006.
6. Centers for Disease Control and Prevention. Childhood obesity facts. http://www.cdc.gov/healthyyouth/obesity/facts.htm.

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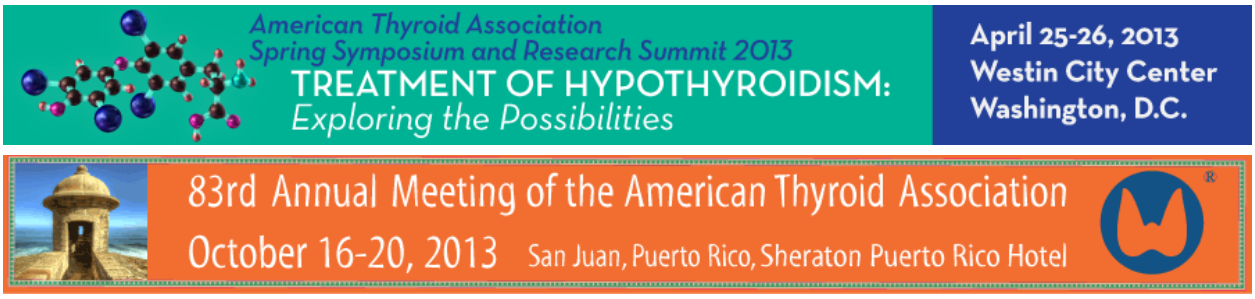

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