Clinical THYROIDOLOGY

JUNE 2012
VOLUME 24 • ISSUE 6

AMERICAN THYROID ASSOCIATION
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THYROIDOLOGY

VOLUME 24 • ISSUE 6 JUNE 2012

Newer TSH Receptor Antibody Assays May Sometimes Be a Useful Additional Factor for Predicting which Graves' Patients Will Remain in Remission when Antithyroid Drugs are Stopped

Giuliani C, Cerrone D, Harii N, Thornton M, Kohn LD, Dagia NM, Bucci I, Carpentieri M, Di Nenno B, Di Blasio A, Vitti P, Monaco F, Napolitano G. A TSHR-LH/CGR chimera that measures functional thyroid-stimulating autoantibodies (TSAb) can predict remission or recurrence in Graves' patients undergoing antithyroid drug (ATD) treatment. J Clin Endocrinol Metab. April 6 2012 [Epub ahead of print]. doi: 10.1210/jc.2011-2897.

SUMMARY

Background

Many factors are reportedly associated with the likelihood that Graves' disease will relapse after antithyroid drug treatment is discontinued, but most do not occur with the consistency needed to be very useful clinically. The current paper assessed the ability of several different assays of TSHR antibody levels to predict remission or relapse. Two cell lines (HEK293 and the commercial Thyretain CHO) used "Mc4," a modified human TSHR DNA sequence with a part of its extracellular domain replaced by the similar domain present in the rat LHR. Changing this sequence eliminated a region that was thought to bind some TSHR-blocking antibodies. Predictions based on assays using these two cell lines were compared with predictions based on a commercial ELISA that detects both stimulating and blocking antibodies that compete with the anti-TSHR monoclonal M22. Four authors of the article indicated competing interests concerning the Mc4 assays.

Methods

Serum samples were obtained from 40 female and 15 male patients with Graves' disease, before and after antithyroid drugs were given for 12 to 48 months at the Chieta University Endocrinology Clinic. Serum obtained at the initial diagnosis was assayed using HEK239 cells that expressed Mc4 plus one of three different cAMP response element-luciferase reporters, and all patients needed to have an above-normal TSHR antibody level based on this assay. All patients had symptoms of hyperthyroidism, a diffuse goiter or ophthalmopathy, a high serum FT_4, an undetectable TSH, an enlarged thyroid on ultrasound with a hypoechoic image, or increased uptake on a radioiodine scan. Of the 55 patients, 28 had

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remained in remission for 12 to 168 months after the drugs had been withdrawn, 12 had relapsed 2 to 36 months after the drugs had been withdrawn, and 15 remained on antithyroid drugs because of evidence of persistent disease.

Serum samples on 42 patients were available for two additional assays: CHO cells expressing Mc4 plus a cAMP reporter (Thyretain, Diagnostic Hybrids, Athens, OH) and biotin-labeled monoclonal M22 that binds to unoccupied sites on hTSHR coated on ELISA plates (RSR Ltd., Pentwyn, Cardiff, United Kingdom). Assay variability was reduced by averaging three assays of duplicates of each sample. (Note that neither of these commercial assays were the automated versions reviewed in the January 2012 issue of Clinical Thyroidology.)

Results

The mean TSHR antibody level (based on the HEK Mc4 assay) was significantly lower in the group of patients who remained in remission as compared with the combined results of those who relapsed plus those in whom drug treatment was continued. The antibody levels present in most of the individuals who remained in remission had fallen into the normal range on all three assays at the time the drugs were discontinued (22 of 28 on the HEK Mc4 assay, 16 of 22 on the Thyretain CHO cells, and 19 of 22 on the M22 ELISA). However, this also means that when drugs were discontinued, the levels were still high in a substantial minority of patients who nonetheless did remain in remission (in 6, 6, and 3 patients, respectively). On the other hand, only a few of the patients who relapsed had normal antibody levels (2 of 12, 2 of 8, and 2 of 8, respectively). Most of the patients who had persistent disease and suppressed TSH levels maintained high antibody levels (15 of 15, 11 of 12, and 9 of 12, respectively). Thyroid volume at the end of treatment was significantly less in those who remained in remission: about 15±7 ml versus 25±13 ml in those who relapsed and versus 30±10 ml in those who remained on therapy.

Conclusions

All three assays seemed have some utility in predicting remission or relapse in patients with Graves' disease; based on the relatively small number of patients available, no major differences were apparent. A larger prospective study on all patients with hyperthyroidism (not preselected for a positive Mc4 assay) might provide more definitive results and could provide a deeper insight into possible mechanisms of immunoglobulin actions on the TSHR.

ANALYSIS AND COMMENTARY

If a patient with Graves' disease has taken antithyroid drugs for a year or more, the thyroid has shrunk to or below normal size, and the TSHR antibody level (measured with one of the newer assays) has normalized, then the odds favor a durable remission. However, even when the authors tried to adjust the cutoff values on the tests, the predictions sometimes were wrong. Other factors beyond thyroid size and the levels of TSH and TSHR antibodies are also important in determining whether or not a case will remain in remission. The TSHR is not simply a spigot that regulates the level of cAMP production. The intensity and duration of stimulation by TSH and/or various antibodies can affect posttranslational modifications, multimer formation, internalization, and associations with other cellular proteins (1, 2). Moreover, even if there were an assay that could measure all stimulating, blocking, and neutral antibodies separately, relapse rates would still be affected by differences in patients with regard to the development of self-tolerance, the thyroid's responsiveness to TSH and anti-TSHR antibodies, and the body's many responses to changing levels of thyroid hormone, as well as in the degree of autoimmune damage to the thyroid and the ability to repair that damage.

— Stephen W. Spaulding, MD

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REFERENCES

1. Kursawe R, Paschke R. Modulation of TSHR signaling by posttranslational modifications. TRENDS Endocrinol Metab 2007;18:199-207. Epub May 23, 2007.

2. Werthmann RC, Volpe S, Lohse MJ, Calebiro D. Persistent cAMP signaling by internalized TSH receptors occurs in thyroid but not in HEK293 cells. FASEB J 2012;26:2043-8. Epub January 30, 2012. doi: 10.1096/fj.11-195248.

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A Large Nationwide Survey of Patients Hospitalized with Thyroid Storm Has Been Used to Develop a Different Approach to Characterizing the Disease

Akamizu T, Satoh T, Isozaki O, Suzuki A, Wakino S, Iburi T, Tsuboi K, Monden T, Tsuyoshi Kouki T, Otani H, Teramukai S, Uehara R, Nakamura Y, Nagai M, Mori M. Diagnostic criteria and clinico-epidemiological features of thyroid storm based on a nationwide survey. Thyroid. April 11, 2012 [Epub ahead of print]. doi: 10.1089/thy.2011-0334.

SUMMARY

Background

Thyroid storm occurs in association with a broad spectrum of nonthyroidal conditions. It can appear in patients without previous hyperthyroidism, but it can also appear after decades of hyperthyroidism, particularly in patients who have not been consistent in taking their antithyroid drugs. Severe stress is often cited as a connection between these various diseases, but the mechanisms involved in thyroid storm remain mysterious; its rarity and the difficulty of establishing just which patients should be given the diagnosis add to the problem. Advances in surgical management and in the care of critical illness are believed to have reduced mortality from thyroid storm. This Japan-wide retrospective survey represents a substantial step forward in the systematic study of this nebulous condition. All Japanese university hospitals, all special thyroid or emergency hospitals, and all hospitals over 500 beds were surveyed, along with a randomized size-scaled selection of smaller hospitals with fewer beds. Approximately 20% of all Japanese hospitals were contacted in 2009, and about half responded to the question of whether or not they had seen any suspected storm cases among the patients with thyrotoxicosis who were admitted to their hospitals in the past 5 years. Based on the 541 reports of possible cases, patient-specific data were requested and analyzed, which resulted in 356 patients deemed to have storm occurring in 2004 to 2008. Data from 133 control patients who had thyrotoxicosis but did not have thyroid storm were also collected from the authors' clinics for several months for comparison.

Methods

The authors initially developed diagnostic criteria by reviewing case reports (22 from PubMed, 1992 to 2005; 77 from the Japanese Ichushi database, 1983 to 2005; as well as data from 7 unpublished cases) and comparing them with the 133 control patients with thyrotoxicosis who did not have storm. The authors slightly revised the criteria after reviewing the data from the 356 new cases. "Definite" storm cases were defined as patients who had an elevated FT_3 or FT_4 at the time storm developed, and who had one of two sets of features.

(A) Patients who had specific Central Nervous System (CNS) manifestations (restlessness, delirium, psychosis/mental aberrations, somnolence/lethargy, convulsions, or a score of 14 or less on the Glasgow Coma Scale or of 1 or more on the Japan Coma Scale) needed to have only one of 4 additional conditions: either a temperature of 38°C or higher; tachycardia of 130 beats per minute or higher; severe congestive heart failure (CHF; New York Heart Association Class IV or Killip class III, with pulmonary edema, moist rales over more than half the lung field, or cardiogenic shock); or gastrointestinal (GI)/hepatic manifestations (diarrhea, nausea/vomiting, or a bilirubin above 3 mg/dl). (Interestingly, abdominal pain was not a criterion, although perforation of the GI tract was the direct cause of death in 2 cases).

(B) Patients without CNS manifestations (other than anxiety or agitation) had to have the requisite high FT_3/FT_4, plus at least 3 of the 4 additional conditions listed under A. "Suspected" storm cases were defined as patients having at least two of the four conditions listed under A, plus a high FT_3/FT_4; or else they could have all the criteria for "definite" storm, but the requirement for a concurrent serum FT_3/FT_4 value

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was forgiven if other data confirming the existence of thyrotoxicosis was present.

The authors compared the results of their "fever/tachycardia/GI/CHF with or without CNS" scoring method with the modified Wartofsky scoring system that sums up the numerical severity for each of five parameters—CNS manifestations, GI dysfunction, tachycardia, temperature, and CHF—plus gives an additional 10 points for atrial fibrillation or a precipitating event (1). (The total numerical score gives an estimate of the likelihood of storm: unlikely, impending, likely, or highly likely). Most of the "suspected" cases had a Wartofsky score in the "likely" range, and most of the "definite" cases were scored as "highly likely," although there were some remarkably discrepant cases.

Results

As expected, the levels of TSH, FT_4 and FT_3 did not differ between control patients with hyperthyroidism and the 356 patients with definite or suspected storm. There were 38 deaths in total. Mortality in the 282 classified as definite storm was the same as in the 74 classified as suspected storm: about 10%. A cause of death was identified in 77% of patients; the most common cause in both definite and suspected storm was multiple organ failure (24%), followed by CHF (21%), respiratory failure (8%), arrhythmia (8%), disseminated intravascular coagulation (DIC; 5%), and GI perforation (5%). Multiple-logistic-regression analysis indicated that patients who had multiple organ failure had a 10-fold increase in the risk of death, while those who either had shock or DIC had a 4-fold increase in the risk of death; again, there was no difference between definite and suspected cases. Triggering factors for storm were identified in 70%; the five commonest triggers were irregular use or discontinuation of antithyroid drugs (34%), infection (24%), and diabetic ketoacidosis, severe emotional stress, or trauma (3% each). Thyrotoxicosis had been present for less than a month before storm developed in about 45 patients, but storm also developed in patients in whom thyrotoxicosis had been present for decades. The mortality rate for patients with a bilirubin over 3 mg/ml was 32%, with multiple organ failure 24%, and with severe CHF 21%. Atrial fibrillation occurred in 38% of all patients with storm, but was present in almost 53% of fatal cases.

Conclusions

Simple regression analysis suggested that CNS manifestations and/or CHF might be associated with increased mortality, but multiple regression analysis did not confirm an association. Patients with multiple organ failure were 10 times as likely to die, and those with shock or DIC had a 4-fold increased risk of death. Perhaps a future prospective study using the diagnostic criteria outlined could help us make clinical decisions earlier, although the variety of possible associated diseases probably would hinder establishing standard clinical protocols.

ANALYSIS AND COMMENTARY

When one encounters a noncompliant patient with Graves' disease who has marked tachycardia, diaphoresis, and nausea and diarrhea or who has a severe respiratory infection, signs of sepsis, heart failure, or mental changes, the safest thing to do is hospitalize the patient and provide empiric therapy. Not uncommonly, the patient will turn out to be "a tropical depression" and not a full blown "storm," but making a decision on hospitalization based on a point score or on the number of organ systems that show abnormalities remains a long way in the future.

The current study excluded any cases in which an underlying disease appeared to be responsible for fever (e.g., pneumonia), impaired consciousness

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(e.g., psychiatric or cerebrovascular disorders), heart failure (e.g., acute myocardial infarction), or liver failure (e.g., viral hepatitis or acute liver failure). However, such diseases clearly can trigger thyroid storm. The updated Wartofsky approach (1) indicates that when it is not possible to distinguish whether a finding is due to an intercurrent illness or to thyrotoxicosis, the higher point score is given so as to favor empiric therapy. In addition to the stringency of the selection criteria in the current study, its spectrum of cases may differ from those in other parts of the world, since Japan has a high level of dietary iodine intake, while toxic nodular goiter is rare. The authors required documentation of serum FT_3/FT_4 levels to prove thyrotoxicosis, but severe illnesses are well known to reduce T_3 levels, and patients with thyroid storm who are already receiving antithyroid drugs could have been excluded. It is interesting that a single cutoff value of a temperature over 38°C (which isn't that uncommon in patients with garden-variety Graves' disease) was useful, while only the most severe grade of CHF was useful in distinguishing cases of storm, and that atrial fibrillation, abdominal pain, and agitation were not useful. Finally, the division of cases into definite and suspected seems to have been relatively unrewarding, since both groups had the same mortality rate. This ambitious and exciting study extends hope not only for prospective studies, but also for studies on organ-specific toxicities of thyroid hormones and for cooperative clinical studies to analyze the tsunami of cytokines and chemokines that doubtless occur in these unusual patients.

— Stephen W. Spaulding, MD

REFERENCES

1. Wartofsky L. Thyrotoxic storm. In: Braverman L, Utiger R, eds. Werner and Ingbar's The thyroid: a fundamental and clinical text. 9th ed. Philadelphia: Williams & Wilkins, 2005:651-7.

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Neurodevelopment at 5.5 Years of Age Is Lower in Very Preterm Infants Born of Mothers with Mild TSH Elevation at Term, but Paradoxically, Lower Maternal FT_4 Was Associated with Better Neurodevelopment

Williams F, Watson J, Ogston S, Hume R, Willatts P, Visser T, Scottish Preterm Thyroid Group. Mild maternal thyroid dysfunction at delivery of infants born ≤34 weeks and neurodevelopmental outcome at 5.5 years. J Clin Endocrinol Metab. April 4, 2012 [Epub ahead of print]. doi:10.1210/jc.2011-2451.

SUMMARY

Background

Mild maternal thyroid dysfunction during early pregnancy is associated with poor neurodevelopment in affected offspring. Most studies are population-based or are smaller populations of term/late preterm infants. No studies were found that focused on earlier preterm infants. The objective of the authors was to describe the relationship between mild maternal thyroid dysfunction at delivery of infants born at 34 weeks and neurodevelopment at 5.5 years of age.

Methods

The Millennium study recruited women and infants between 1998 and 2001. Infants born at or before 34 weeks' gestation were recruited from all Scottish neonatal intensive care units; 662 women agreed to participate. The authors measured maternal and cord thyroid hormones, TSH, TgAb, TPOAb, and TBG levels at delivery; maternal TSH, FT_4, and T_4, and the association with McCarthy Scale scores adjusted for 26 confounders of neurodevelopment were available for 143 women and 166 children (122 singletons, 19 twins, and 2 triplets). The mean (±SD) gestation was 30.8±2.4 weeks. Neurodevelopment was assessed when children were 5.5 years old, using the McCarthy Scales, which provide six distinct measures: the general cognitive index (GCI), that is derived from verbal, perceptual performance, and quantitative subscales and separate memory and motor scales. Women with known thyroid disease were excluded from the analysis.

Results

The scores for memory and motor scales were both lower than the population norms (t = 2.27, P= 0.02, and t= 3.68, P = 0.0003, respectively). Following adjustment for 26 of the major confounding factors for neurodevelopment, each milliunit-per-liter increment of maternal TSH level at delivery was associated with a significant 3.2-point, 2.1-point, and 1.8-point decrement in general cognitive index, verbal subscale, and perceptual performance subscale, respectively. Higher maternal TSH levels were not associated with significant decrements in the other scales. Mild maternal hypothyroidism (TSH levels ≥3 mU/L) was evident in 27% of the women. McCarthy scores for children born to women with mild hypothyroidism were generally lower than those born to euthyroid women; the GCI, verbal, and perceptual performance scores were significantly lower by 13.5, 7.5, and 7.8 points, respectively. The results of the regression analyses using the data from only the singleton deliveries were similar to those using the full data set. BAPM (British Association of Perinatal Medicine) level 1, which is a proxy for severity of infant condition, was the confounding variable most frequently associated with large decrements in the McCarthy Scales.

Few women (8%, n = 11) were classified as having mild hypothyroxinemia (normal TSH levels), using FT_4 levels ≤11.6 pmol/L. After adjustment, significant associations were found for the general cognitive index, motor scale, and quantitative subscale; each picomole–per-liter decrease in FT_4 was associated with an increase of 1.5, 1.7, and 0.9 points, respectively. Maternal T_4 levels showed little relationship with neurodevelopment. None of the women in this analysis had overt hypothyroidism, but mild hypothyroidism was evident in 27% (n = 38) and there were high levels of TPOAb in 4%, whereas 28% had high TgAb levels.

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Conclusions

The authors found that higher levels of maternal TSH at delivery of infants born at ≤34 weeks' gestation are associated with significantly lower GCI and verbal and perceptual performance subscale scores, and that low maternal FT_4 levels are associated with higher scores on the GCI, quantitative subscale, and motor scale. The association of low maternal FT_4 levels and increased GCI and quantitative subscale (and possibly motor scale) scores is difficult to interpret. The robustness of these findings should be tested in another cohort of women who deliver preterm infants and for whom thyroid hormone data are available for each trimester of pregnancy.

ANALYSIS AND COMMENTARY

Abnormal obstetric and neonatal outcomes have been reported in the literature in the past decade in women with thyroid dysfunction and in euthyroid women affected by chronic thyroiditis. Not all reports agree with regard to the frequency and type of complications. In most of the reported studies, thyroid tests, including serum TSH, FT_4, and thyroid antibodies were measured at different weeks in the first trimester of pregnancy or early in the second trimester. Therefore, the incidence of complications was based on a single determination of thyroid function early in pregnancy. It is well recognized that in untreated euthyroid women suffering from autoimmune thyroid disease, serum TSH tends to increase with progression of pregnancy, with the potential development of hypothyroidism; also, there is a significant decline in antibodies titers starting in the second half of gestation (1, 2). Preterm delivery (PTD; at or before 37 weeks' gestation) and very preterm delivery (VPTD; at or before 34 weeks' gestation) are complications frequently reported in women with hypothyroidism and those with euthyroid chronic thyroiditis. PTD is the leading cause of perinatal morbidity and mortality in the United States. In a review of six published reports, an association between thyroid antibody elevations and preterm birth was found in only three of them (3). Adverse child neuropsychological outcomes due to maternal thyroid disease (dysfunction or presence of thyroid autoantibodies) have been reported (4, 5).

Williams et al.'s study of the effect of thyroid dysfunction and prematurity on children's neurodevelopment outcome differed from previous studies; they compared the neurodevelopmental outcome at age 5.5 years of infants born before 34 weeks' gestation in mothers with untreated mild thyroid dysfunction diagnosed at the time of delivery. No information is given about whether these mothers had hypothyroidism early in pregnancy or whether it developed with progression of gestation. Several aspects of the study are of interest; one of them is the lower percentage of women with positive TPOAb (4%) as compared with women with high TgAB titers (28%), while the prevalence in women delivering at term in their cohort was 10% and 9%, respectively. The authors did not speculate or comment about the potential significance of these findings but acknowledge that this deserves confirmation by future investigations. Another point of interest is the unusually high proportion, 21% of women in the Millennium cohort, with TSH levels at delivery of ≥3 mU/L (27% for the women reported in this analysis). The authors speculated "that these Scottish women are mildly iodine deficient, maintaining a euthyroid state for FT_4 and T_4 by slightly raised TSH levels," but they acknowledge that this interpretation is subject to challenge, since other studies have shown normal serum TSH levels and low FT_4 in areas of iodine deficiency.

An interesting observation by the authors is the potential "protective" effect of lower maternal levels

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of FT_4 on child neurodevelopment. Although they admitted that there is little information about whether levels of thyroid hormones differ between women who deliver prematurely or at term, they offered their own unpublished data showing that maternal serum FT_4 levels measured at 31 to 34 weeks' gestation are different in women who deliver at that point (15.4 pmol/L) as compared with women who go on to deliver at ≥37 weeks (11.7 pmol/L). The authors suggested that high maternal FT_4 levels at critical points of pregnancy may be detrimental to fetal/infant brain development. It could be helpful, as they pointed out, to use adjusted maternal thyroid hormone levels, in late pregnancy, according to gestational age, similar to interpretation of thyroid tests in newborns.

The authors' multiple observations need to be confirmed but offer the opportunity for applying different approaches in the evaluation of morbidities to an evolving and relatively new field of endocrine fetal–neonatal and child thyroid pathology.

— Jorge H. Mestman, MD

References

1. Glinoer D, Riahi M, Grün JP, Kinthaert J. Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. J Clin Endocrinol Metab 1994;79:197-204
2. Negro R, Formoso G, Mangieri, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 2006;91:2587–91. Epub ahead of print April 18, 2006.
3. Haddow JE, Cleary-Goldman J, McClain MR, Palomaki GE, Neveux LM, Lambert-Messerlian G, Canick JA, Malone FD, Porter TF, Nyberg DA, et al. Thyroperoxidase and thyroglobulin antibodies in early pregnancy and preterm delivery. Obstet Gynecol 2010;116:58-62.
4. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, et al. Maternal function during early pregnancy and cognitive functioning in early childhood: the generation R study. J Clin Endocrinol Metab 2010;95:4227-34. Epub June 9, 2010.
5. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. Clin Endocrinol (Oxf) 2010;72:825-9.

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TSH Secreting Tumors Can Be Cured By Long Term Octreotide Treatment

Fliers E, van Furth WR, Bisschop PH. 2012. Cure of a thyrotrophin (TSH)-secreting pituitary adenoma by medical therapy. Clin Endocrinol. April 6, 2012 [Epub ahead of print]. doi: 10.1111/j.1365-2265.2012.04405.x.

SUMMARY

Background

A measurable serum TSH level in the presence of frankly increased FT_4 and FT_3 is a very unusual situation. It should direct the diagnosis either toward thyroid hormone resistance or toward a pituitary adenoma secreting TSH (TSHoma). The main differential diagnosis of TSHomas is resistance to thyroid hormones (generalized, peripheral, or central) (1, 2). In TSHomas, the basal α-subunit has a tendency to be slightly increased but not in resistance to thyroid hormones. MRI and a TRH test that shows a minimal increase of serum TSH and of its α-subunit can distinguish the two conditions. Genetic screening of the beta T_3 receptor will usually establish the diagnosis of thyroid hormone resistance, even though there are some cases that have not been elucidated genetically. The TSHoma described here can be considered a classical case on grounds of both biologic and imaging results. The patient has been treated for 4 years with octreotide with shrinkage of the tumor and return to normal thyroid function even after stopping treatment.

Method and Results

A 19-year-old male patient, who was diagnosed with a TSHoma, presented with frank hyperthyroidism but measurable serum TSH levels (TSH, 4.3 mU/L, FT_4, 52 pmol/L, and total T_3, 4.9 nmol/L). An MRI revealed a macroadenoma with suprasellar extension. Visual field defects were not reported. The TRH test showed no response of serum TSH, and the α-subunit also did not increase. There was no associated hypersecretion of growth hormone or prolactin. Within 4 months after treatment with octreotide, thyroid function normalized and a repeat MRI showed a marked decrease of the tumor. Following these encouraging results the patient was maintained on octreotide treatment for 4 years, when MRI images indicated the disappearance of the tumor. Then the treatment was stopped. The patient remained has euthyroid and there was no evidence of recurrence of the pituitary tumor as documented by MRIs during the next 4 years.

Conclusions

In many centers, treatment of TSHomas with octreotide or dopaminergic agonists is the first-line treatment, with the aim of obtaining control of the hyperthyroid state and facilitating the neurosurgical approach. Several cases have been reported in which surgery was delayed or declined, so that the patients remained on conservative treatment over the years. The success in terms of control of hyperthyroidism is usually good, but few data are available on the size of the tumors (3). Therefore, the main interest of this case lies in the facts that during treatment the tumor disappeared and that even 4 years after stopping treatment there was no recurrence of either hyperthyroidism or of the tumor. It therefore adds a new brick favoring the strategy of conservative treatment of these tumors.

ANALYSIS AND COMMENTARY

The patient described here had, like many patients with TSHomas, a large macroadenoma with suprasellar extension. If there had not been a very rapid response to the drug treatment, the patient would certainly have had surgery. Yet the follow-up indicated that the pituitary tumor had indeed been cured. This patient is probably unique for having been observed

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during several years after stopping treatment without recurrence. A similar course is known for other pituitary tumors, most typically for prolactinomas, that may be definitely cured with conservative treatment (4).

It is interesting that several conservatively treated TSHomas have been followed by other groups without surgical intervention (3). It is not known whether some of these patients have been taken off treatment without recurrence of the tumor. Possibly some of these cases will join the list started by the present case of being cured after long-term drug treatment. Obviously, the question remains whether one of the two treatments, octreotide or dopaminergic agents, has superior efficacy. To my knowledge this is not known. The number of published cases of TSHomas is still small, and it is certainly advisable to treat these patients with great prudence.

— Albert G. Burger MD

REFERENCES

1. Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. Endocr Rev 1993;14:348-99.
2. Refetoff S. Resistance to thyroid hormone: one of several defects causing reduced sensitivity to thyroid hormone. Nat Clin Pract Endocrinol Metab 2008;4:1.
3. Kienitz T, Quinkler M, Strasburger CJ, Ventz M. Long-term management in five cases of TSH-secreting pituitary adenomas: a single center study and review of the literature Eur J Endocrinol 2007;157:39-46.
4. Colao A, Di Sarno A, Cappabianca P, Di Somma C, Pivonello R, Lombardi G.Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. N Engl J Med 2003;349:2023-33.

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Subclinical Central Hypothyroidism Can Be Diagnosed by Echocardiography

Doin FC, Rosa-Borges M, Martins MR, Moisés VA, Abucham J. Diagnosis of subclinical central hypothyroidism in patients with hypothalamic-pituitary disease by Doppler echocardiography. Eur J Endocrinol 2012;166:631-40. Epub January 20, 2012.

SUMMARY

Background

Central hypothyroidism is a condition resulting from reduced secretion of normal TSH or secretion of biologically inactive TSH in patients with lesions in the hypothalamic–pituitary area. The diagnosis is based on low FT_4 with low, normal, or even slightly elevated serum TSH with presumably less biologic activity because of altered glycosylation (1). Subclinical primary hypothyroidism is a well-recognized entity diagnosed by elevated serum TSH with normal FT_4 measurements. The authors proposed that there is a diagnostic entity of subclinical central hypothyroidism even though the FT_4 is in the normal range. They based their diagnosis of subclinical central hypothyroidism on echocardiographic parameters. This concept is consistent with numerous studies that have shown cardiac abnormalities in patients with subclinical primary hypothyroidism that is reversed by treatment with levothyroxine (2).

Methods

The authors studied 35 patients with hypothalamic–pituitary disease; they excluded patients with hypertension or coexisting primary cardiac disease as well as acromegaly and Cushing's disease because of the cardiac effects of these disorders. Ten of the cases of hypothalamic–pituitary disease were classified as overt central hypothyroidism because the FT_4 was low. These authors also studied 28 controls and 20 patients with overt primary hypothyroidism. The patients and controls had echocardiographic assessment to determine the isovolumic contraction time (ICT) and the ejection time (ET) and calculated the myocardial performance index (MPI).

Results

Based on statistical evaluation of the echocardiography, the cutoff values for the diagnosis of hypothyroidism were: ICT >53 msec (sensitivity, 83% [95% confidence interval {CI}, 65 to 94]; specificity, 96% [CI, 82 to 100]); ICT/ET ratio >0.18 (sensitivity, 83% [CI, 65 to 94]; specificity, 96% [CI, 82 to 100]); and MPI >0.46 (sensitivity, 90% [CI, 74 to 98]; specificity, 93% [CI, 77 to 99]). The patients with overt central hypothyroidism had alterations in echocardiographic parameters that were similar to those of primary hypothyroidism with prolongation of ICT and increased MPI.

Using echocardiographic assessment, hypothyroidism was diagnosed in 14 of the 25 patients with hypothalamic–pituitary disease who had normal FT_4, and these patients were classified as subclinical central hypothyroidism. Patients with the diagnosis of hypothyroidism were treated with levothyroxine to raise the FT_4, including not only those with overt primary or central hypothyroidism but also those with subclinical primary and subclinical central hypothyroidism. In those with subclinical central hypothyroidism, the mean FT_4 increased from a baseline of 0.96 to 1.38 ng/dl (normal range, 0.7 to 1.54). T_4 therapy significantly decreased all diagnostic echocardiographic parameters in both subclinical primary and subclinical central hypothyroidism and corrected 28 of 29 abnormal parameters in subclinical primary hypothyroidism and 21 of 29 abnormal parameters in subclinical central hypothyroidism.

Conclusions

Echocardiography can be used to make the diagnosis of subclinical central hypothyroidism in patients with hypothalamic–pituitary disease.

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ANALYSIS AND COMMENTARY

The authors make a convincing claim that echocardiography will diagnose tissue hypothyroidism in patients with subclinical thyroid disease, both primary and central. The parameters generally reverted to normal with levothyroxine treatment, but whether this may have occurred in euthyroid subjects is a moot point. They note that deficiencies in growth hormone and sex steroids were distributed nearly equally between those who did and those who did not have subclinical central hypothyroidism, leading them to conclude that these hormones did not affect the echocardiographic diagnosis. Coexistence of cardiac disease is the main limitation in the use of echocardiography for making the diagnosis of hypothyroidism.

The parameters that were used in the study can easily be calculated when standard echocardiography is performed, and thus this technique can be used for diagnosis of hypothyroidism; but echocardiography is an expensive test for making this diagnosis. Most endocrinologists use the FT_4 level and clinical judgment based on experience to make the diagnosis of central hypothyroidism. If there are other pituitary deficiencies and the FT_4 is in the low normal range, a trial of levothyroxine is worthwhile, with the goal of raising its level to the midnormal range. In order to avoid precipitating an adrenal crisis, evaluation of the ACTH-adrenal axis and treatment of adrenal insufficiency is mandatory before commencing thyroxine therapy.

— Jerome M. Hershman, MD

References

1. Beck-Peccoz P, Amr S, Menezes-Ferreira MM, Faglia G, Weintraub BD. Decreased receptor binding of biologically inactive thyrotropin in central hypothyroidism: effect of treatment with thyrotropin-releasing hormone. N Engl J Med 1985;312:1085-90.
2. Biondi B, Palmieri EA, Lombardi G, Fazio S. Subclinical hypothyroidism and cardiac function. Thyroid 2002;12:505-10.

Clinical THYROIDOLOGY
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The AJCC TNM Staging Underestimates Risk in Young Patients with More Aggressive Differentiated Thyroid Cancer

Tran Cao HS, Johnston LE, Chang DC, Bouvet M. A critical analysis of the American Joint Committee on Cancer (AJCC) staging system for differentiated thyroid carcinoma in young patients on the basis of the Surveillance, Epidemiology, and End Results (SEER) registry. Surgery. April 11, 2012 [Epub ahead of print].

SUMMARY

Background

The differentiated thyroid cancer (DTC) staging system of the American Joint Committee on Cancer (AJCC) uses age for staging the patient. Patients less than age 45 with distant metastases are stage II, while patients age 45 or older with metastases are stage IV. Although age is linked to prognosis, it may be too optimistic to classify younger patients in this way. This study examined the effect of age and disease extent in the AJCC staging system on mortality using survival data from the Surveillance, Epidemiology, and End Results (SEER) Program from 1973 to 2005 in order to determine whether the risk stratification accurately portrayed outcomes of DTC for young patients.

Methods

The SEER data set includes data on the primary tumor, demography, spread, histology, and mortality across multiple geographic regions. The examiners included patients with DTC as their only malignancy between 1973 and 2005. They used Cox multivariate proportional-hazards models to generate a relative risk of death by any cause with 95% confidence intervals, controlling for sex, race, marital status, histology, surgical and radiation treatment, age at diagnosis, and stage.

Results

The SEER database had sufficient data to generate the tumor–node–metastasis (TNM) stage using the AJCC Cancer Staging Manual, 6th edition for 49,240 patients. The mean (±SD) age was 44.6±15.5 years. In the multivariate analysis, increasing age correlated with increased mortality. There was an approximately 50% increased mortality for every decade from age 40 to age 90. The magnitude of the age effect was greater in women than in men.

In patients less than age 45, the mortality of stage II was 11-fold greater than that of stage I, but in those age 45 or older there was no significant increase in risk between stages I and II. Survival of patients less than 45 years old with stage II was worse than older stage II patients who had tumors of 2 to 4 cm confined to the thyroid gland. When the TNM staging for age 45 or older was applied to those less than age 45, there was an increase of mortality hazard ratio for those now reclassified as stage III or IV based on lymph-node involvement and tumor spread outside the thyroid but without distant metastases.

Conclusions

The presence of regional spread and distant metastatic DTC bears prognostic significance for all ages. Under current AJCC guidelines, young patients with metastatic thyroid cancer may be understaged.

ANALYSIS AND COMMENTARY

There are many different staging systems for thyroid cancer (1, 2), but in recent years there has been increasing acceptance of the AJCC TNM system as the most convenient and widely applicable for DTC. This excellent paper confirms the adverse effect of increasing age on mortality in patients with DTC. Another recent paper reported increased cause-specific mortality in Japanese patients over age 60 who had papillary thyroid cancer (3). However, the TNM staging system's emphasis on age, as the current paper points out, underestimates mortality in young patients. This

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underestimate is widely known by practitioners who use more aggressive therapy in young patients with extrathyroidal spread, especially those with distant metastases. Although older work emphasized the lack of effect of spread to lymph nodes on mortality in young patients (4), other analyses concluded that positive lymph nodes were associated with more frequent recurrences (5). The current study demonstrated a significant adverse effect of nodal disease on survival in both age groups.

It should be noted that almost one-fourth of newly diagnosed DTC patients in the SEER database were between ages 40 and 50 years. This makes the age 45 threshold for staging somewhat arbitrary. Limitations of the study are that the SEER database did not contain data on specific histology or vascular invasion. The study did not analyze recurrence, a more frequent event than mortality in patients with DTC. The study did not control for the effect of treatment on survival. In fact, the paper uses the term radiation rather than specifically denoting therapy with radioiodine-131. All in all, I must agree with the authors' recommendation that the AJCC system needs to be revised, with more specific and detailed staging for young patients.

— Jerome M. Hershman, MD

References

1. Dulgeroff AJ, Hershman JM. Medical therapy for differentiated thyroid carcinoma. Endocr Rev 1994;15:500-15.
2. Jukkola A, Bloigu R, Ebeling T, Salmela P, Blanco G. Prognostic factors in differentiated thyroid carcinomas and their implications for current staging classifications. Endocr Relat Cancer 2004;11:571–9.
3. Ito Y, Miyauchi A, Kihara M, Takamura Y, Kobayashi K, Miya A. Relationship between prognosis of papillary thyroid carcinoma patient and age: a retrospective single-institution study. Endocr J. February 29, 2012 [Epub ahead of print].
4. Cady B, Rossi R, Silverman M, Wool M. Further evidence of the validity of risk group definition in differentiated thyroid carcinoma. Surgery 1985;98:1171-8.
5. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.

Clinical THYROIDOLOGY
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A Conservative Approach Based on Measurement of Calcitonin Permits Delay in Surgical Treatment of RET Mutation–Positive Medullary Carcinoma

Elisei R, Romei, C, Renzini G, Bottici V, Cosci B, Molinaro E, Agate L, Cappagli V, Miccoli P, Berti P, Faviana P, Ugolini C, Basolo F, Vitti P, Pinchera A. The timing of total thyroidectomy in RET gene mutation carriers could be personalized and safely planned on the basis of serum calcitonin: 18 years experience at one single center. J Clin Endocrinol Metab 2012;97:426-35.

SUMMARY

Background

Medullary thyroid cancer (MTC) can occur as part of three different syndromes—MEN2A, MEN2B, and familial medullary cancer (FMTC). A delay of the diagnosis until lymph-node metastases and local infiltration are present has dramatic consequences, including a high death rate. Early diagnosis is therefore mandatory. In 1993, a marker for the germline mutation of RET proto-oncogene was discovered and, as a consequence, genetic screening of families with cases of medullary thyroid cancer with or without hyperparathyroidism and/or pheochromocytoma was rapidly accepted as a standard procedure. In patients carrying the mutation (gene carriers, GC), early prophylactic thyroidectomy was recommended. In 2009, the ATA published guidelines using a staging system to define different risk levels (1). Early operation remained the treatment of choice. The present prospective study from a large center in Italy proposed that the indications for thyroidectomy be modified, taking into account in GC patients basal and pentagastrin (PG)-stimulated serum calcitonin levels.

Methods and Results

During an observation period of 18 years, 103 MTC families were followed (28 MEN2A, 8 MEN2B, and 67 FMTC); 472 subjects were investigated. Screening of all families revealed 140 subjects with germline mutations (for the individual mutations, see the original text); 89 subjects had already been diagnosed and had undergone thyroidectomy before entering the study, and 84 subjects agreed to participate in the study.

Three groups were formed. In group I, the worst cases, basal calcitonin levels were increased and the PG test was pathological. In these subjects neck ultrasound revealed suspicious tissue in 20 of 21 cases. In group II, basal calcitonin levels were normal (<10 pg/ml) but PG tests were positive. Included in this group are patients whose initial PG tests were negative but became positive several years later (mean, 4 years). Group III had both normal basal and PG tests. Nevertheless, even in this group, neck ultrasonography revealed some abnormal tissue in approximately 30% of cases (no details are given). Interestingly, there was no correlation between the classification according to the calcitonin levels and the criteria of severity according to the guidelines of the American Thyroid Association.

Of the GC patients, 53 underwent total thyroidectomy with central-lymph-node neck dissection. Of particular interest was the finding that the value of 60 pg/ml of calcitonin was a highly specific and sensitive indicator of lymph-node involvement, which is a most critical prognostic factor. In patients with calcitonin levels between 10 and 60 pg/ml, MTCs at operation were small and confined to the thyroid. In group II, with calcitonin levels of 10 pg/ml or less but a pathological PG test, the tumors were small (maximum, 0.7 cm in diameter), with no lymph-node involvement. In four initially negative cases that became positive within 4 years, the tumors were between 0.1 and 0.3 cm. The remaining subjects with normal calcitonin levels did not show evidence of MTC at follow-up and are currently still under annual control. Thus, particularly in patients below 16 years of age, thyroidectomy could be delayed without compromising the prognosis.

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Conclusions

The study shows that in GC patients, an alternative strategy to the initial thyroidectomy can be safely adopted by using basal and PG-stimulated calcitonin levels as criteria; in countries where PG is not available, this test can be replaced by calcium gluconate infusions (2, 3). A basal value of calcitonin of 60 pg/ml or more indicates significant disease necessitating intervention. In contrast, if calcitonin levels are 10 pg/ml or less, tumor involvement is minimal. Another group has put the critical level at 30 pg/ml (4). Obviously, patients need an annual complete clinical evaluation. Thanks to this strategy, surgery can be delayed, which is particularly beneficial in young patients. In none of these GC cases was there rapid evolution from minimal disease to a severely progressive disease.

ANALYSIS AND COMMEMTARY

The screening of families of GC patients usually leads rapidly to early thyroidectomy in affected patients. Very often, thyroidectomies are performed in children as young as 5 years of age. Surgery in such young children is not without risks. To meet concerns, the guidelines of the ATA propose a more differentiated approach. The present study describes probably the most conservative approach proposed so far. It is certainly appreciated by the parents and the children carrying this disease. There are some minor caveats. At present, the number of patients studied is still small and one has to be aware of possible GC carriers that progress rapidly from a stage of normal basal and stimulated calcitonin levels to severe disease. In the present study the 4 cases that evolved in this way, had only minimal cancers at operation, which is so far reassuring. Another caveat are those patients who were lost to follow-up. Probably the clinician will feel safer if the patient had thyroidectomy before being lost to follow-up. Finally, in group III, with no pathological basal and stimulated calcitonin levels, neck ultrasound revealed pathological structures in one third of all subjects. Unfortunately, the authors give no further information about this disturbing observation. The reader is left to conclude that the finding was interpreted as being totally different from anything resembling MTC. If not so, the whole message of the article would have to be put into question.

— Albert G. Burger, MD

REFERENCES

1. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JF, Pacini F, Ringel MD, Schlumberger M, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.
2. Elisei R, Pinchera A. Advances in the follow-up of differentiated or medullary thyroid cancer. Nat Rev Endocrinol. April 3, 2012 [Epub ahead of print]. doi: 10.1038/nrendo.2012.38.
3. Colombo C, Verga U, Mian C, Ferrero S, Perrino M, Vicentini L, Dazzi D, Opocher G, Pelizzo MR, Beck-Peccoz P, Fugazzola L. Comparison of calcium and pentagastrin tests for the diagnosis and follow-up of medullary thyroid cancer. J Clin Endocrinol Metab 2012;97:905-13. Epub December 14, 2011.
4. Rohmer V, Vidal-Trecan G, Bourdelot A, Niccoli P, Murat A, Wemeau JL, Borson-Chazot F, Schvartz C, Tabarin A, Chabre O, et al. Prognostic factors of disease-free survival after thyroidectomy in 170 young patients with a RET germline mutation: a multicenter study of the Groupe Francais d'Etude des Tumeurs Endocrines. J Clin Endocrinol Metab 2011;96:E509-18. Epub December 29, 2010.

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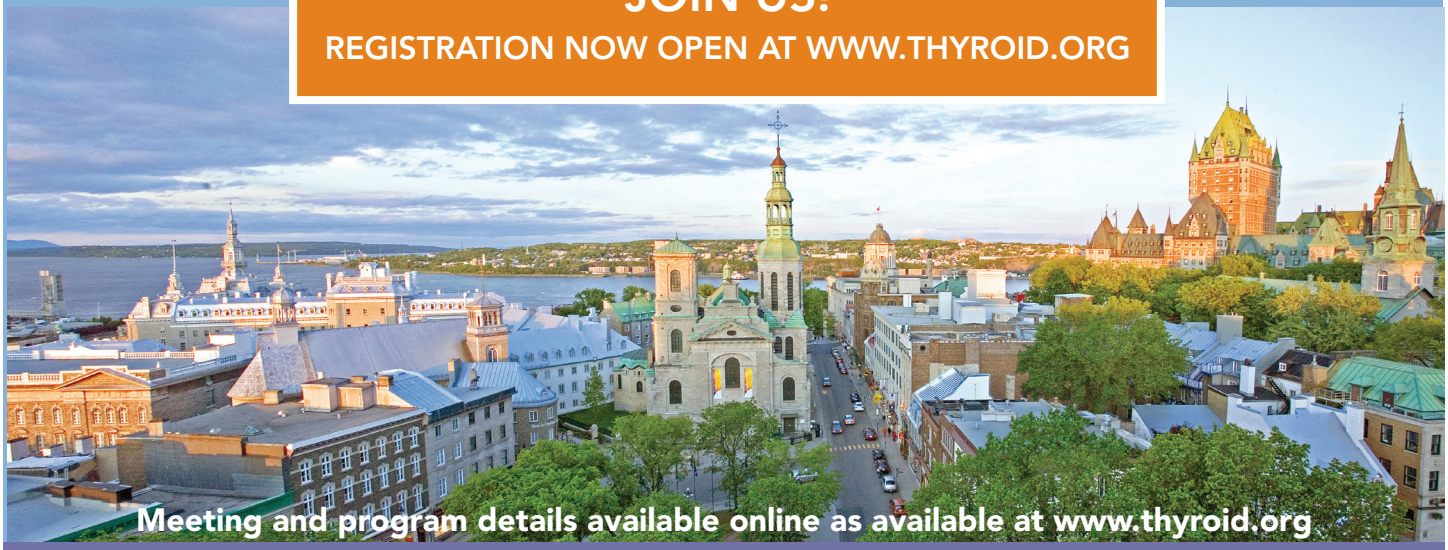

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