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Clinical Thyroidology

EDITOR'S COMMENTS

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CLINICAL THYROIDOLOGY STATISTICS We are happy to report that there are more than 4,300 subscribers to *Clinical Thyroidology* online. The articles in Volume 21, Issue 1 to 7 have been viewed more than 27,000 unique times. Our subscribers include 2,502 MDs and 202 PhDs, as well as members from 196 different specialties or areas of interest from 118 countries. We are grateful that so many are using *Clinical Thyroidology*.

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WHATS NEW The last page now has a set of references to REVIEWS & HOT ARTICLES which contains references to important reviews and very recent articles that look especially important to the Editors.

EDITOR'S CHOICE ARTICLES are particularly important studies that we recommend you read in their entirety.

We welcome your feedback and suggestions on these changes.

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Ernest L. Mazzaferri, MD, MACP
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Antithyroperoxidase antibody and antithyroglobulin antibody positivity during the first trimester of pregnancy is a major risk for perinatal death

Männistö T, Vääräsmäki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Järvelin MR, Suvanto-Luukkonen E. Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. J Clin Endocrinol Metab 2009;94:772-9.

SUMMARY

BACKGROUND Undiagnosed or insufficiently treated thyroid dysfunction affects a considerable number of pregnant women. The suspected adverse outcome on the offspring is currently the subject of considerable concern and extensive discussion. There are, however, only a few large prospective studies evaluating the effect of maternal thyroid dysfunction on offspring. Moreover, the observations are inconsistent.

METHODS The prospective Northern Finland Birth Cohort comprises 99% of live births in the region of Northern Finland. The study comprises all births with a calculated term from July 1 through June 30, 1986, that was drawn from the two northernmost provinces of Finland, with 9362 mothers and 9479 children in the target population. This study included only 9247 singleton pregnancies from the present study of 9479 children who had been followed since the 12th gestational week. The first questionnaire on demographic, biologic, health behavioral, and socioeconomic characteristics of the mothers and families covered the period up to the 24th gestational week, when the mothers were enrolled in the study if they were still pregnant. A second questionnaire covered maternal health and health behavior during pregnancy and the perinatal period. The third questionnaire contained items about pregnancy complications and diseases, delivery, and neonatal outcome and was completed in the maternity hospitals by the attending midwives. All women gave birth at the hospital.

Data were collected on thyroid hormones, thyrotropin (TSH), free triiodothyronine (FT_3), free thyroxine (FT_4), and autoantibodies (thyroid peroxidase antibody [TPOAb] and thyroglobulin antibodies [TgAb]). The lower limits of detection were 0.0025 μIU/ml for TSH, 5.1 pmol/L for FT_4, 2.3 pmol/L for FT_3, 1.0 IU/ml for TPOAb, and 1.0 IU/ml, for TgAb. The mean (±SD) gestational age at sampling was 11±3.6 weeks, and only samples drawn before or at the 20th gestational week were accepted (98% of the samples).The study population was large enough to create reference values applicable to the study cohort and to take into account the effect of freezing and storage.

The subjects with thyroid dysfunction were divided into four groups with respect to thyroid hormone levels: group A (clinical hypothyroidism) with TSH over the 95th percentile and FT_4 under the 5th percentile (n = 54); group B (subclinical hypothyroidism) with TSH over the 95th percentile and FT_4 between the 5th and 95th percentiles (n = 224); group C (subclinical hyperthyroidism with TSH under the 5th percentile, FT_4 between the 5th and 95th percentile (n = 204); and group D (clinical hyperthyroidism) with TSH under the 5th percentile and FT_4 over the 95th percentile (n = 204). The reference group had TSH between the 5th and 95th percentiles and FT_4 between the 5th and 95th percentiles. Groups A to D were compared with the reference group.

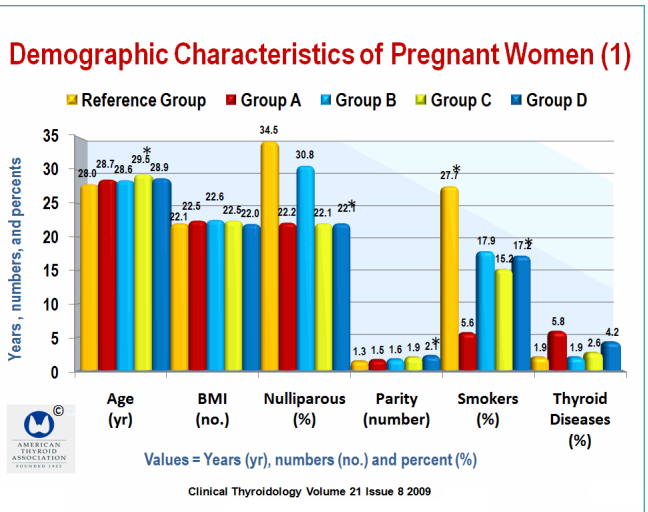

Figure 1. This figure shows the demographic characteristics of pregnant women. Values are means, numbers, or percents. The reference group had a TSH between the 5th and 95th percentiles and an FT_4 between the 5th and 95th percentiles; group A (clinical hypothyroidism) had a TSH over the 95th percentile, and FT_4 under the 5th percentile; group B (subclinical hypothyroidism) had a TSH over the 95th percentile, and FT_4 between the 5th and 95th percentiles; group C (subclinical hyperthyroidism) had a TSH under the 5th percentile and FT_4 between the 5th and 95th percentiles; group D (clinical hyperthyroidism) had a TSH under the 5th percentile, and FT_4 over the 95th percentile. *P<0.05 when comparing groups A to D together or separately with the reference group or comparing the antibody-positive group with the antibody-negative group. Body-mass index is the weight in kilograms divided by the square of the height in meters. Derived from Table 2 in Männistö et al.

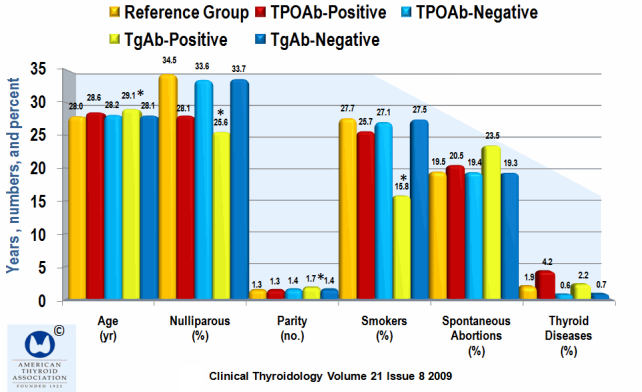

Figure 2. This figure shows demographic characteristics of pregnant women. *P<0.01. See Figure 1 for further legend details. Derived from Table 2 in Männistö et al.

Mothers were considered to be TPOAb- or TgAb-positive if the concentrations of the antibody were over the 95th percentile.

All data concerning the mothers and their obstetric histories were obtained from the questionnaires. The data on perinatal outcomes comprised gestational age, preterm delivery (birth at <37th gestational week); birth measurements (birth weight small for gestational age [SGA] and large for gestational age [LGA]; birth length, ponderal index [birth weight/birth length^3], and head circumference); Apgar scores; perinatal mortality (stillborns and early neonatal deaths <7 days after birth); neonatal deaths; malformations; and umbilical-cord length.

RESULTS The demographic data of the mothers in each group did not differ substantially from that in the whole cohort according to their thyroid hormone and antibody status. However, there were significant differences among those in the reference group and in groups A to D in maternal age, body-mass index, parity, smoking habits and the prevalence of previous thyroid disease. The mothers in group C were older; those in group B were heavier; and those in groups B, C, and D had higher parity; groups A, B, and C included fewer smokers, and groups A, B, and D more often had a history of thyroid disease than mothers in the reference group (Figure 1). TPOAb-positive women were older and had higher parity and fewer were smokers, as compared with the TgAb-negative mothers, and for these reasons the results were adjusted for maternity age and parity. Infants in group A had a higher mean ponderal index than infants of the reference group. Absolute and relative placental weights were higher in group A (Figure 2). There were no significant differences in any of the perinatal outcomes when group B was compared with the reference group (Figure 3).

The infants in group C less often had Apgar scores of 7 or less at 5 min than infants in the reference group (Figure 3) and had a risk of 0.4 for having low Apgar scores at 5 min when compared with the reference group (Figure 4). In group D, both absolute and relative placental weights as well as absolute birth weight and the number of LGA infants were higher than in the reference group (Figure 3).The infants in group D were at a 2.7-fold greater risk for being LGA as compared with infants in the reference group (Figure 4), but the risk was no longer significant after adjusting for maternal age and parity. Mothers who were TPOAb-positive more often had both low-birth-weight infants and LGA infants than did TPOAb-negative mothers (Figure 5). No differences were observed in the frequencies of SGA infants in groups A to D. Infants of TPOAb-positive mothers were at a 2-fold higher risk for being LGA and a 1.7-fold higher risk for low birth weight (Figure 4). The offspring of TPOAb- and TgAb-positive mothers had a 2- to 3-fold greater perinatal mortality than those of the antibody-negative mothers (Figures 4 and 5). In the TPOAb-positive group, four of seven perinatally deceased infants were born very preterm (before gestational week 28), and in the TgAb-positive group, three of six were born very preterm. Mothers who were TgAb-positive had an almost 2-fold risk for having children showing nonocephalic presentation at birth (Figures 4 and 5). An evaluation of the independent effect of maternal underweight (body-mass index ≤20) found that it was not associated with any

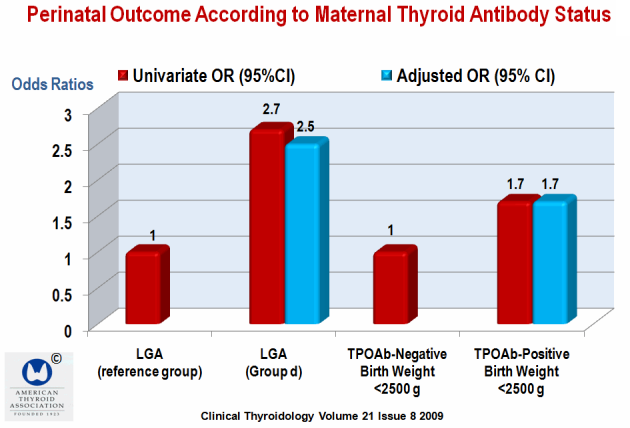

Figure 3. Odds ratios (ORs) with 95% confidence intervals (CIs) showing perinatal outcome of children grouped according to maternal thyroid hormone status. Derived from Table 4in Männistö et al. See legend in Figure 1 for further legend details. LGA is large growth weight for gestational age.

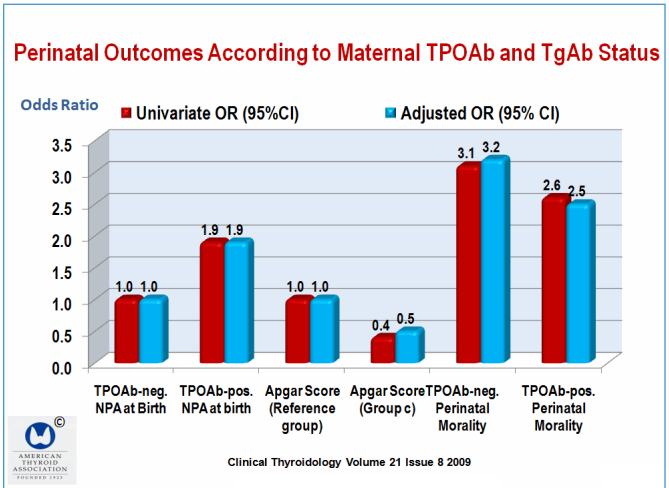

Figure 4. Estimated risks of perinatal outcomes with maternal antibody status. CI = confidence interval; NPA = noncephalic presentation; OR = odds ratio. Derived from Table 4 in Männistö et al.

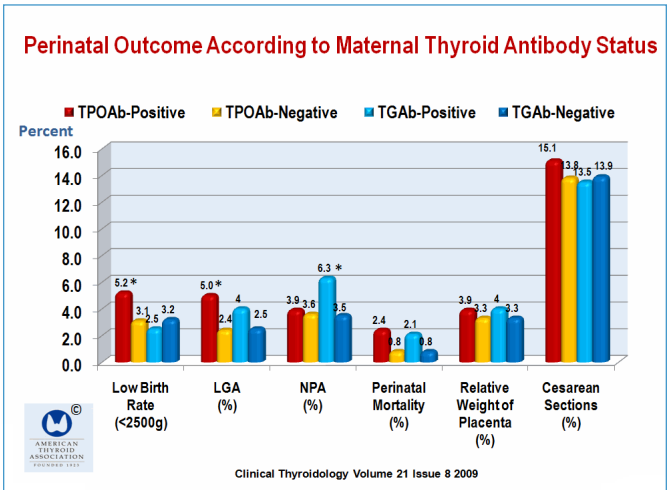

Figure 5. Prenatal outcome according to maternal thyroid antibody status. *P = 0.05 comparing TPOAb-positive and TPOAb-negative. Derived from Table 5 in Männistö et al. NPA = noncephalic presentation.

of the adverse perinatal outcomes (Figure 4). However, maternal overweight was a significant risk factor (odds ratio, 1.7 1.2 to 2.5) for LGA, but there was no association between maternal overweight and perinatal mortality and low birth weight. Thyroid hormone status appears to be less influential in this regard

CONCLUSION Antithyroperoxidase antibody and antithyroglobulin antibody positivity during the first trimester of pregnancy is a major risk for perinatal death, although thyroid-function status, as such, is not associated with this risk.

COMMENTARY

The authors of this study found only four prospective cohort studies in which the effect of thyroid hormone status on perinatal outcome has been investigated. Allen et al. (1), in a study of 9403 women with singleton pregnancies, found 209 with serum TSH concentrations of 6 µIU/ml or higher (2.2%). The fetal death rate (3.8%) was significantly higher in the pregnancies with high serum TSH levels than in the women with a serum TSH less than 6 mU/L (0.9%; odds ratio, 4.4). The authors concluded that, from the second trimester onward, the major adverse obstetrical outcome associated with an elevated TSH in the general population is an increased rate of fetal death. The authors suggested that if thyroid-replacement treatment avoided this problem this would be another reason to consider population screening.

In a study by Casey et al. (2) of 25,756 women who underwent thyroid screening and delivered a singleton infant, 17,298 (67%) women enrolled for prenatal care at 20 weeks of gestation or less, and 404 (2.3%) of this group had subclinical hypothyroidism. The study found that pregnancies in women with subclinical hypothyroidism were 3-fold more likely to be complicated by placental abruption (relative risk, 3.0). Preterm birth, defined as delivery at or before 34 weeks of gestation, was almost 2-fold higher in women with subclinical hypothyroidism (relative risk, 1.8). Casey et al. speculated that the previously reported reduction in intelligence quotient of offspring of women with subclinical hypothyroidism may be related to the effects of prematurity.

In another study, Matalon et al. (3) investigated the results of pregnancy in women with hypothyroidism, comparing outcomes of singleton pregnancies of patients with and without hypothyroidism. During the study period, they found that among 139,168 singleton deliveries, 0.8% (n = 1102) were in patients with hypothyroidism. Multivariate analysis found that the following risk factors were significantly associated with hypothyroidism: fertility treatments, recurrent abortions, diabetes mellitus, previous cesarean section and advanced maternal age. There were no significant differences in pregnancy complications, such as placental abruption, preterm deliveries or postpartum hemorrhage, between the euthyroid and hypothyroid groups; however, patients with hypothyroidism had higher rates of cesarean deliveries (20.1% vs. 11.5%, P<0.001). This association remained significant even after controlling for confounders, such as diabetes mellitus, previous cesarean section, fertility treatments, recurrent abortions, and advanced maternal age. When hypothyroidism was diagnosed and treated before pregnancy, there were no significant differences in perinatal outcomes, including birth weight <2500 g (10.4% in the hypothyroidism group vs. 9.5% in the euthyroid control group [P = 0.159]) and Apgar score <7 at 5 minutes (0.8% vs. 0.6%, P = 0.312). Perinatal mortality (1.4% vs. 1.3%; P = 0.95) did not differ between the two groups. The authors concluded that appropriate treatment of maternal hypothyroidism with levothyroxine is not associated with adverse perinatal outcome.

Männistö et al. found that maternal thyroid autoantibody positivity but not thyroid hormone status at the end of the first trimester was associated with elevated perinatal mortality. Mothers who were positive for TgAb who had large for gestational age (LGA) children, whereas mothers who were also positive for TPOAb more often had both low-birth-weight infants and LGA infants than occurred in TPOAb-negative mothers. Still, no differences were observed in the frequencies of SGA infants between the groups with and without TPOAb. Infants of TPOAb-positive mothers had a 2-fold risk for being LGA and a 1.7-fold risk for low birth weight. Moreover, the offspring of TPOAb- and TgAb-positive mothers had a 2- to 3-fold higher risk of perinatal mortality than those of mothers who were antibody-negative. A study by Negro et al. (4) found that TPO-Ab positivity was significantly related to preterm delivery, the rate of which decreased with levothyroxine treatment. These findings, as well as those reported by Casey et al. (2), suggest that an increased rate of preterm delivery among TPO-Ab-positive women may be related to impaired thyroid function. The mothers with high TSH combined with low FT_4 levels also showed a slight tendency to have an increased rate of preterm delivery, but this was not the case when FT_4 levels were normal. Männistö et al. suggest that antibodies could possibly explain this because 50% of the mothers with high TSH and low FT_4 levels were antibody-positive. Männistö et al. suggest that thyroid dysfunction cannot be confirmed in their study and that the role of autoimmunity and thyroid autoantibodies in preterm deliveries requires further research.

This is an important study that likely will generate more studies of this important issue.

— Ernest L. Mazzaferri, MD, MACP

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There is an increased incidence of hyperthyroidism in Down syndrome that should be regularly tested for at all ages

Goday-Arno A, Cerda-Esteva M, Flores-Le-Roux JA, Chillaron-Jordan JJ, Corretger JM, Cano-Perez JF. Hyperthyroidism in a population with Down syndrome (DS). Clin Endocrinol (Oxf) 2009;71:110-4.

SUMMARY

BACKGROUND Hypothyroidism is the most common thyroid abnormality in Down syndrome (DS), with a prevalence of almost 50%; however, whether hyperthyroidism might be more prevalent than usual in DS is unknown, as only sporadic cases of hyperthyroidism with DS have been reported in the literature. The aim of this study was to assess the prevalence, cause, clinical characteristics, pathology, treatment, and evolution of hyperthyroidism in a population with DS.

METHODS This is a retrospective study of 1832 medical records from the Catalan Down Syndrome Foundation in Spain, from which data for the study cohort were obtained from January 1991 through February 2006. The records contained the following information: patient age, anthropometric measurements, clinical symptoms and signs of hyperthyroidism such as insomnia, decreased heat tolerance, profuse sweating, nervousness, hyperdefecation, and weight loss. In addition, the findings on physical examination included the thyroid examination, heart rate, eye signs of hyperthyroidism, and distal tremor. Laboratory information was available concerning the serum thyrotropin (TSH), serum free thyroxine (FT_4), total triiodothyronine (T_3), serum thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb), and thyroid-stimulating immunoglobulin (TSI). Family histories of thyroid disorders and other autoimmune disorders were also obtained. All patients with hyperthyroidism had a technetium-99m (99mTc) thyroid scan, and some had a neck ultrasound examination, depending on the attending physician. Patients with hyperthyroidism were reassessed at 2-month intervals.

RESULTS Among 1832 individuals with DS, 12 had hyperthyroidism, 5 of whom were male and 7 of whom were female, with ages ranging from 10.9 to 28.9 years. The mean weight was 42.5 kg (93.5 lb; range, 24.5 to 68.8 [53.9 to 151.4]), and the mean height 142.6 cm (56.1 in.; range, 124.4 to 153 [49 to 60.2]).

DIAGNOSIS The diagnosis of hyperthyroidism was made clinically, and not as a consequence of thyroid-function screening tests that were performed annually in all individuals with DS. Symptoms leading to a diagnosis of hyperthyroidism were decreased heat tolerance and sweating (n = 11, 92%), increased emotional irritability (n = 10, 83%), a mean weight loss of 4.7 kg (25.1 lb) in the previous months (n = 10, 83%), palpitations (n = 9, 75%), insomnia (n = 7, 58%), distal tremor (n = 7, 58%), increased bowel frequency (n = 4, 33%), and sore eyes (n = 3, 25%). Mean heart rate at the time of diagnosis was 94 beats/min (range, 80 to 132) (Figure 1). The thyroid examination revealed diffuse thyroid enlargement in all the patients, which, according to the World Health Organization criteria, were grade 2 goiters in 11 patients and grade 3 in 1 patient (Figure 2). Two patients (17%) presented with exophthalmos.

LABORATORY TESTS All patients had undetectable serum TSH concentrations with elevated median serum FT_4 concentrations of 63.7 pmol/L (4.93 ng/dl), with a range of 24.5 to 158.6 (1.89 to 12.3; reference range, 9 to 19.4 pmol/L [0.69 to 1.51 ng/dl]), and elevated mean serum total T_3 concentrations of 11.2 nmol/L (727 ng/dl), with a range of 2.8 to 22.8 (182 to 1480; reference range, 1.2 to 2.5 [77.9 to 162]). Mean serum TSI concentrations were increased to 128.1 U/L (range, 10 to 620; reference range, <10 IU/L]). TPOAb elevations were present in 11 of 12 patients (92%), and serum TgAb elevations were found in 4 of 12 patients (33.3%).

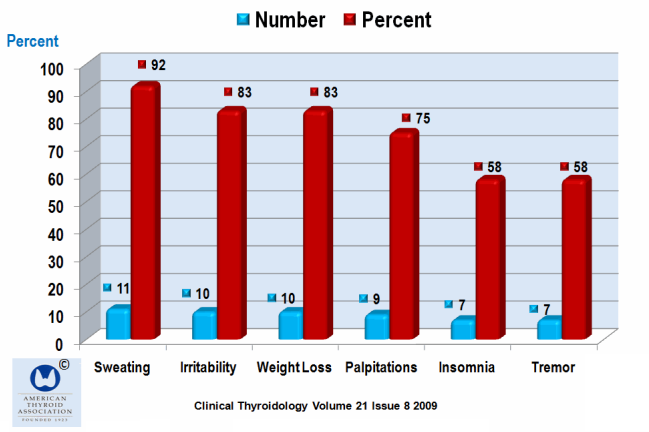

Figure 1. This figure shows the main symptoms of hyperthyroidism in patients with Down Syndrome

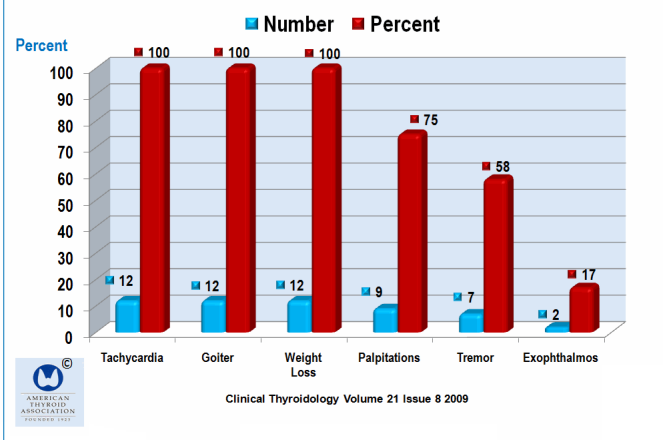

Figure 2. This figure shows the main physical findings of hyperthyroidism in patients with Down Syndrome

A 99mTc scan showed diffuse thyroid uptake in all patients, which was suggestive of Graves' disease. A diffuse goiter was found in the two patients who had neck ultrasonography.

EPIDEMIOLOGY The incidence of Graves' disease in the DS population was 43 cases per 10,000 persons per year, as compared with 24 cases per 100,000 persons per year in the population of Spain. In a Danish study, the incidence of juvenile thyrotoxicosis was 0.79 per 100,000 persons. All were lower than the incidence rates of Graves' disease in the DS population

TREATMENT For all patients, the initial therapy was 10 mg of carbimazole three times daily, which was adjusted according to the results of thyroid-function tests. Carbimazole withdrawal was attempted in all patients, but all experienced a relapse. After a mean of 40.3 months (range, 10 to 96) only 2 patients continued to take carbimazole, because their families rejected treatment with radioactive iodine (^{131}I). After relapse, the other 10 patients were treated with ^{131}I, which resulted in hypothyroidism requiring levothyroxine therapy in all patients.

OUTCOME During the first 6 months of therapy, the mean weight increased by 11.4 kg (3.1 lb) and the mean height by 5.3 cm (21 in.). Among the patients with hyperthyroidism, 2 had celiac disease, and there was 1 case each of myasthenia gravis, vitiligo, and alopecia areata. There were no cases of diabetes mellitus.

CONCLUSION There is an increased incidence of hyperthyroidism in DS that often fails to achieve remission with antithyroid drugs, subsequently requiring radioiodine treatment.

COMMENTARY

DS is the most common genetic form of mental retardation and the leading cause of certain birth defects and medical conditions (1). The association of DS with thyroid disorders has been recognized for decades. Over 25 years ago, reports (2) described overt thyroid dysfunction in DS. At present, up to 54% of individuals with DS are reported to have thyroid disorders, the prevalence of which increases with age (3). However, most of the literature has focused on hypothyroidism in DS, which has consequently resulted in the recommendation to regularly screen individuals with DS for hypothyroidism (4). However, Goday-Arno found 27 articles in the literature from 1974 through 2005 that reported a total of 46 cases of hyperthyroidism in DS. Among this group, Graves' disease was documented in 10 cases, while the cause was uncertain in the other 17. In seven of the articles, carbimazole and propylthiouracil were used to treat hyperthyroidism, but the details of drug therapy were not described in the others. Only 2 patients were treated with ^{131}I and 2 had subtotal or total thyroidectomy.

A much clearer picture emerges in the group of patients with DS described by Goday-Arno et al. All cases of hyperthyroidism were due to Graves' disease. Only 16% of the patients had ophthalmopathy, a rate lower than that reported for the general population with Graves' disease. The authors suggest that this may be the result of the young age of many of the patients in this study and the fact that none were smokers. Otherwise, the clinical characteristics of Graves' hyperthyroidism in the patients with DS had features of hyperthyroidism that were similar to those found in the general population with Graves' disease.

Why none of the patients in the study achieved remission with antithyroid drugs is not entirely clear, but in contrast to the usual insidious onset of autoimmune hypothyroidism, the cases reported by Goday-Arno had overt thyrotoxicosis at the time of diagnosis, with obvious symptoms and overt biochemical features of hyperthyroidism. Still, the most striking feature of these cases is that none of the 12 patients responded to carbimazole or propylthiouracil despite being on antithyroid drugs for as long as 96 months. After an average of 40 months on antithyroid drugs, all of the patients failed to achieve remission and all but 2 were thus treated with ^{131}I. The 2 patients not so treated remained on antithyroid drugs because the parents did not want their children treated with ^{131}Iand none were treated with surgery. Almost 30% of the DS population has high levels of antithyroid antibodies (5), but there were no cases of hyperthyroidism due to autoimmune disorders, commonly referred to Hashitoxicosis. Yet, among the patients with hyperthyroidism, there were 2 cases of celiac disease and 1 case each of myasthenia gravis, vitiligo, and alopecia areata, without any cases of diabetes mellitus.

The major finding in this study is that the incidence of hyperthyroidism among individuals with DS is significantly greater than that in the general population, underscoring that physicians must be aware of the problem and perform thyroid-function tests at all ages in patients with DS.

— Ernest L. Mazzaferri, MD, MACP

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The onset of MPO-ANCA–associated vasculitis with antithyroid drugs is both rare and unpredictable, but is more common with PTU

Noh JY, Yasuda S, Sato S, Matsumoto M, Kunii Y, Noguchi Y, Mukasa K, Ito K, Ito K, Sugiyama O, Kobayashi H, Nihojima S, Okazaki M, Yokoyama S. Clinical characteristics of myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis caused by antithyroid drugs. J Clin Endocrinol Metab 2009;94:2806-11.

SUMMARY

BACKGROUND The presence of myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) in a patient in whom respiratory failure developed while taking propylthiouracil (PTU) was first described in 1992. Since then, only a few reports of MPO-ANCA–associated vasculitis with PTU and methimazole (MMI) have been published, thus providing sparse clinical descriptions of this disorder. The aim of this study was to determine the incidence of MPO-ANCA–associated vasculitis in a large number of patients taking PTU or MMI and to analyze the clinical characteristics of this condition, including its symptoms, and the association of antithyroid drugs and their doses to clinically apparent MPO-ANCA–associated vasculitis.

METHODS The study subjects were 92 patients with Graves' disease who had MPO-ANCA–associated vasculitis as an adverse reaction to antithyroid drugs and thus were reported, as required by law in Japan, to Chugai Pharmaceutical, which makes PTU and MMI.

RESULTS Of the 92 patients, 23 (25%) were taking MMI from 1979 through December 2007, 68 were taking PTU (75%) from 1982 through December 2007, and 1 more patient was taking antithyroid drugs, but it was not clear which of the two had been taken. The median age at the onset of the adverse reaction was 46 years (range, 10 to 81), and the ratio of men to women was 20:72. The following data were collected: the type of MPO-ANCA–associated vasculitis, dose of antithyroid drug at the time of vasculitis onset, severity and outcome, duration of treatment from the time of onset, and MPO-ANCA titer. Here and elsewhere, all percentages >1% are rounded to an integer.

The type and frequency of MPO-ANCA–associated vasculitis and its symptoms and organ involvement are shown in Figures 1 and 2. MPO-ANCA–associated vasculitis caused single-organ failure in 41 patients (45%), two-organ failure in 32 patients (35%), three-organ failure in 13 patients (14%), four-organ failure in 2 patients (2%), and was unknown in 4 patients (4%) (Figure 3). The most common combination of two-organ failure was kidneys and respiratory organs, and the most common three-organ failure was kidneys, joints, and skin. Symptoms were severe in 79 patients (86%), moderate in 2 (2%), and mild in 2 (2%); the severity was unknown in 9 patients (10%). (Figure 4). MPO-ANCA–associated vasculitis resolved in 62 patients (67%), caused death in 2 (2%), and caused persistent sequelae in 21 (23%); the outcome was unknown in 7 patients (8%) (Figure 4). Of the two patients who died, one each had been treated with MMI and PTU, and had MPO-ANCA titers of 317 ELISA units (EU) and 489 EU, respectively, and both had kidney and respiratory organ failure. The median MPO-ANCA titer, which was known for 76 of the 92 patients (83%), was 230.5 EU (range, 33 to 5170); and for the remaining 16 patients was recorded only as positive. The MPO-ANCA titer was less than 100 EU in 22 patients (29%), which was considered weakly positive. At the onset of MPO-ANCA–associated vasculitis, the median dose of MMI was 15 mg/day (range, 2.5 to 45), and for PTU 200 mg/day (range, 50 to 450). The median time from starting an antithyroid drug to the onset of MPO-ANCA–associated vasculitis, for all 83 patients for whom these data were available, was 42 months

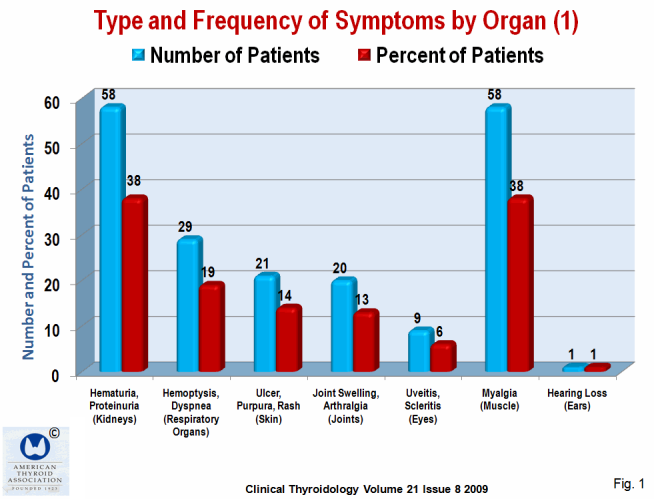

Fig. 1

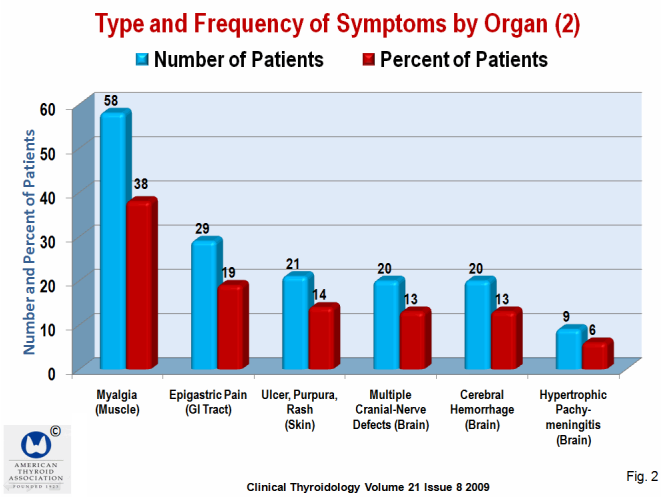

Fig. 2

Figures 1 and 2. These figures show the type and frequency of symptoms and the organs involved with MPO-ANCA–associated vasculitis. GI = gastrointestinal.

(range 1 to 372); it was 60 months (range, 1 to 372) for MMI and 39 months (range, 1 to 132) for PTU, a difference that was not statistically significant between the two drugs. The MPO-ANCA titers were not significantly different among patients with different extents of symptom severity or with multiple organ involvement. The MPO-ANCA titer after discontinuing antithyroid drugs, which was recorded in 50 of the 92 patients, decreased in 40 patients; it decreased to within the reference range in 9 patients, and decreased then increased in only 1 patient, who had crescentic nephritis and arthralgia. Intervention and treatment consisted of discontinuing antithyroid drugs in all patients, and treatment with steroids in 70 patients (76%) and of concurrent therapy with immunosuppressants (cyclosporine and cyclophosphamide) in 17 patients (18%); 6 patients (7%) required renal dialysis.

The annual incidence of MPO-ANCA–associated vasculitis was estimated to be between 0.53 and 0.79 patients per 10,000 in Japan, where the number of patients with Graves' disease is estimated to be between 92,400 and 138,600. Based on the annual shipments of MMI and PTU, the authors believe that the incidence of MPO-ANCA–associated vasculitis for PTU would be 39-fold that of MMI. In the present study, the onset of MPO-ANCA–associated vasculitis occurred within 2 months in 6 patients (7%) and within 1 year in 7 patients (8%) of the 83 patients for whom the time of onset was available, which means that it is impossible to predict when MPO-ANCA–associated vasculitis will occur. Moreover, the dependence of antithyroid-drug dose on MPO-ANCA–associated vasculitis is uncertain.

CONCLUSION The timing of antithyroid drug–induced MPO-ANCA–associated vasculitis is both rare and unpredictable, is increased with PTU, but is not correlated with the dose of antithyroid drugs or the duration of therapy or MPO-ANCA titers, and the symptoms of this complication range from minimal to severe, with multiple organ failure and death in some patients.

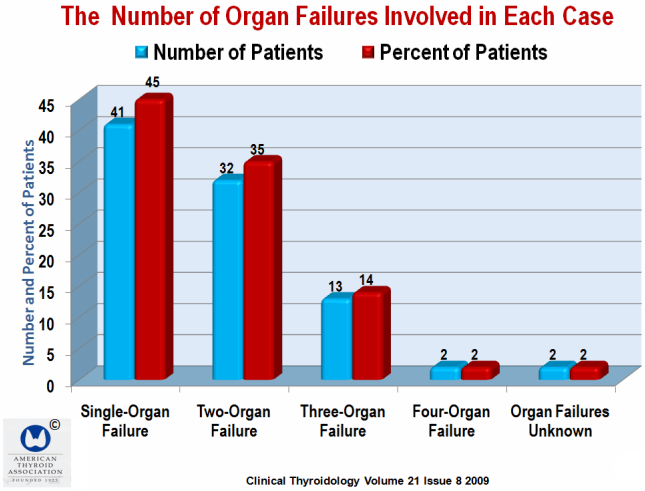

Figure 3. This figure shows the range of organ failure in patients with MPO-ANCA–associated vasculitis.

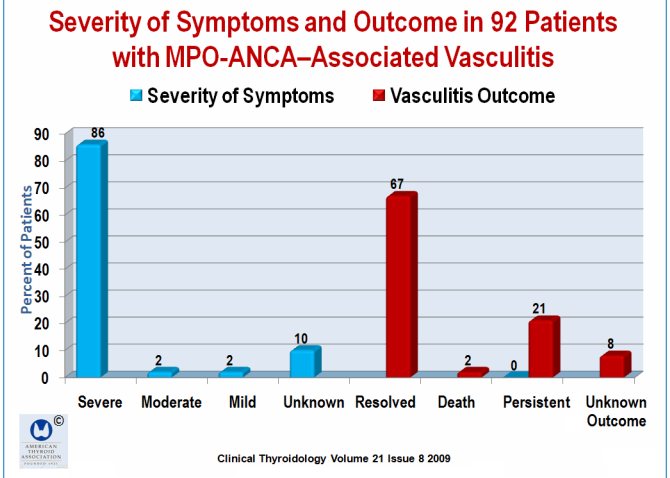

Figure 4. This figure shows the severity of symptoms and the outcomes in 92 patients with MPO-ANCA–associated vasculitis.

COMMENTARY

Vasculitis associated with PTU has been recognized for some time (1-5). Although it has been well known that PTU is associated with MPO-ANCA–associated vasculitis that could spontaneously resolve after cessation of antithyroid drugs with or without immunosuppressive therapy, the treatment strategy for patients with MPO-ANCA–associated vasculitis has remained inconclusive (6), and large studies and long-term outcomes for patients with this complication have been lacking. A recent study by Gao et al. (7) of 15 patients with PTU-induced MPO-ANCA–associated vasculitis who were treated with immunosuppressive agents for less than 12 months and had follow-up for a mean of 55 months (range, 25 to 98) concluded that the long-term outcomes of patients with PTU-induced MPO-ANCA–associated vasculitis were relatively good. The authors recommended that PTU should be discontinued immediately after the diagnosis of MPO-ANCA–associated vasculitis and that immunosuppressive therapy should be used only in patients with vital organ involvements, and that long-term maintenance therapy may not be necessary. However, this was a relatively small study that lacked information concerning the relationships of the dose and duration of antithyroid drugs, and whether MPO-ANCA–associated vasculitis occurs exclusively with PTU was not addressed.

The study by Noh et al. is the largest study of this problem in which data on 92 patients with MPO-ANCA–associated vasculitis were available on key issues concerning this disorder. The symptoms of vasculitis stemmed from involvement of the kidneys, lungs, skin, joints, eyes muscle, gastrointestinal tract, and brain. Of the 92 patients in the study, 45% had single-organ failure, 35% had two-organ failure, most commonly kidneys and respiratory organs, and 14%, had four-organ failure. The most common three-organ failure was the kidneys, joints, and skin. Symptoms were severe in most of the patients (86%), and moderate to mild in the others. MPO-ANCA–associated vasculitis

resolved in 62 patients (67%), caused death in 2 patients (2%), and produced persistent sequelae in 21 patients (23%) in whom the data were known.

The onset of vasculitis occurred within 2 months in 7% of the patients and within 1 year in 8% of the patients in whom a record of the time of onset was available, indicating that it is impossible to predict when vasculitis might occur. Moreover, the type and dose of the antithyroid drug did not correlate with the onset of MPO-ANCA–associated vasculitis. A total of 61 patients had been treated with PTU, and 20 with MMI. The appearance of MPO-ANCA and the onset of MPO-ANCA–associated vasculitis did not always occur together, nor did it correlate with the dose of PTU or MMI. Vasculitis did not necessarily occur in patients who were positive for MPO-ANCA nor did the titer of MPO-ANCA correlate with the severity of vasculitis. Although PTU was calculated to be 39-fold that of MMI among patients with MPO-ANCA–associated vasculitis, the ratio of annual shipments of MMI to those of PTU was about 4 to 1 that might account for the higher ratio of PTU in patients with vasculitis. The authors of this study concluded that there is a need for vigilance in patients being treated with PTU or MMI because the severity and number of organs involved were not correlated with MPO-ANCA titer, and the time of onset of MPO-ANCA–associated vasculitis is so variable, and vasculitis can occur when MPO-ANCA titer is only weakly positive.

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www.thyroid.org/patients/ct/index.html

Whole-body radioiodine retention 72 hours after ^{131}I therapy is paradoxically higher in patients treated with furosemide and potassium chloride than in a control group

Matovic MD, Jankovic SM, Jeremic M, Tasic Z, Vlajkovic M. Unexpected effect of furosemide on radioiodine urinary excretion in patients with differentiated thyroid carcinomas treated with iodine 131. Thyroid 2009;19:843-8.

SUMMARY

BACKGROUND Diuretics are frequently administered to patients receiving therapeutic radioactive iodine (^{131}I) with the intent of accelerating renal elimination of unbound ^{131}I. This is done to reduce the adverse effects of ^{131}I and shorten the hospital stay. The aims of this prospective study were to investigate the influence of furosemide on the urinary excretion of ^{131}I in patients with differentiated thyroid cancer and to investigate whether diuretics are useful in reducing the whole-body retention of ^{131}I and whole-body radiation in patients with thyroid cancer treated with ^{131}I.

METHODS A total of 43 patients with differentiated thyroid cancer (DTC) treated with ^{131}I in the Department of Nuclear Medicine at the Clinical Center in Kragujevac, Serbia, were recruited for study from September 2007 through September 2008. All patients had total thyroidectomy and ^{131}I therapy. Patients with a history of kidney or urologic diseases were excluded from the study. Prior to ^{131}I therapy, all patients had an ultrasound examination that confirmed the presence of both kidneys without evidence of urinary stasis. One day prior to ^{131}I therapy, serum urea and creatinine were measured and found to be within the references ranges of 3.0 to 8.0 nmol/L and 50 to 105 µmol/L, respectively.

Prior to ^{131}I therapy, levothyroxine was discontinued for 4 to 6 weeks to achieve a serum thyrotropin (TSH) concentration of at least 35 µIU/ml. Two weeks prior to ^{131}I, a diagnostic whole-body ^{131}I scan was performed with 3 mCi (111 MBq) of ^{131}I. The mean (±SD) thyroid ^{131}I uptake was only 3.55±3.45% prior to therapeutic ^{131}I that was administered on a fixed-dose approach. Twenty patients were treated with 150 mCi (5.55 GBq) for presumed residual tumor and 23 were treated with 100 mCi (3.7 GBq) for postoperative remnant ablation. Three hours after the administration of ^{131}I, 23 patients were given 20 mg of furosemide and 250 mg of potassium chloride every 8 hours for the next 3 days. Twenty control patients received neither furosemide nor potassium chloride. The patients were divided into two groups, a control group (DTC-CG) and a furosemide group (DTC-FG). After the administration of ^{131}I, the patients collected all their urine and recorded micturition times and urine volumes. A 5-ml urine sample was taken from each patient to measure retention of therapeutic ^{131}I. Average micturition sample fractions (%) were calculated for all patients in both groups for the following time periods: 6, 12, 24, 36, 48, and 72 hours after therapeutic ^{131}I was administered. Individual whole-body radiation measurements were made immediately after ^{131}I administration and 72 hours thereafter, using the same probe on each patient at a distance of 2 meters. The 72-hour whole-body radiation measurements were corrected for ^{131}I decay and were expressed as a fraction (%) of the initial value. After 72 hours, venous blood samples were taken from each patient to measure blood radioactivity by a gamma counter.

RESULTS A total of 43 patients were enrolled in the study, of which 35 were women (81%) and 8 were men (19%), ranging in age from 14 to 17 years (mean [±SD], 45.2±14.41). Of

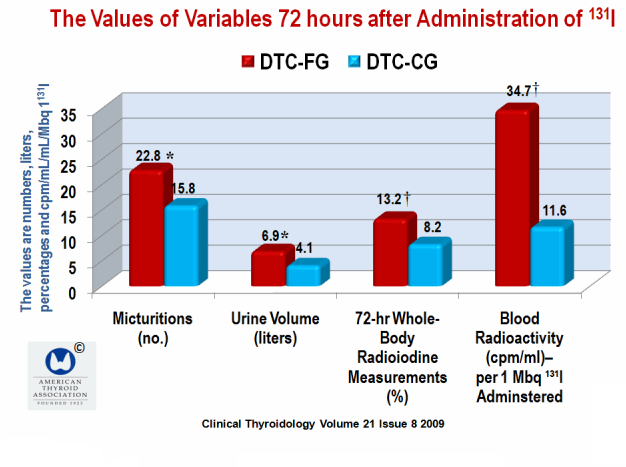

Figure 1. This figure shows that the group treated with furosemide (DTC-FG) micturated significantly more often and passed larger volumes of urine as compared with the control group (DTC-CG). However, the whole-body ^{131}I measurements and blood radioactivity retention were nonetheless higher in the DTC-FG group than in controls. *P <0.001. †P = 0.01

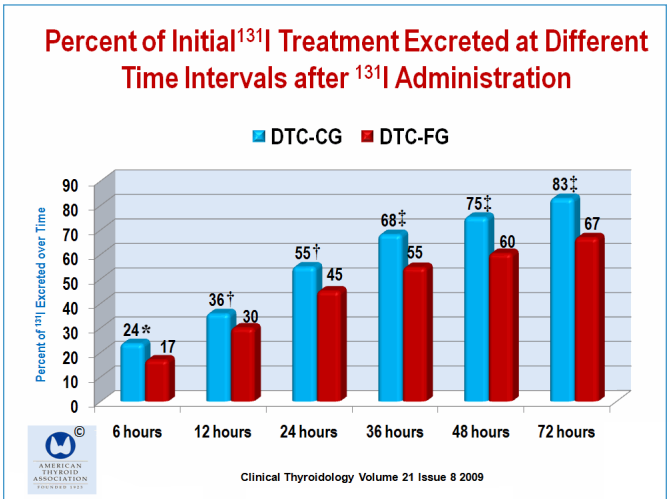

Figure 2. This figure shows the rates of radioiodine excretion from 6 to 72 hours after the administration of ^{131}I. The group treated with furosemide (DTC-FG) excreted significantly less radioiodine over 72 hours as compared with the control group (DTC-CG),*P <0.01, †P < 0.05, ‡P <0.001

this group, 39 had papillary thyroid cancer (91%), 2 had well-differentiated minimally invasive follicular cancer (5%), and 2 had Hürthle-cell carcinoma (5%).The pathological tumor–node–metastases (TNM) classification was T1N0, N1, and Nx in 14, 4, and 3 patients, respectively, and T2N0, N1, and Nx in 2, 1, and 1 patients, respectively; and T4N0, N1, and Nx in 2, 1, and 1 patients, respectively. None had distant metastases.

During the 72-hour period after ^{131}I therapy, patients who were taking furosemide and potassium chloride micturated significantly more frequently than controls. They passed larger volumes of urine and were found to have greater retention of blood radioactivity as compared with controls. Comparing the DTC-FG and DTC-CG groups, the mean number of micturitions 72 hours after the administration of ^{131}I, was 22.81±8.22 vs. 15.83±5.00 ($P<0.001$), the urine volumes were 6865.81±3416.07 vs. 4070.87±2098.68 ml ($P = 0.001$), and the blood radioactivity was 34.66±24.84 vs. 11.64±8.32 counts/min/ml of blood per 0.02 mCi (1 MBq) of ^{131}I ($P = 0.01$) (Figure 1).

Mean ^{131}I excretion in the DTC-CG and DTC-FG groups at 6, 12, 24, 36, 48, and 72 hours after ^{131}I administration was 23.61±8.84 vs. 16.93±8.32% ($P<0.01$) at 6 hours, 35.80±9.92 vs. 28.97±9.39 ($P<0.05$) at 12 hours, 54.89±10.02 vs. 45.05±10.46 at 24 hours ($P<0.05$), 68.10±11.46 vs.54.66±10.55 ($P<0.01$) at 36 hours, 75.14±11.62 vs. 60.39±10.42 ($P<0.001$) at 48 hours, and 82.81±12.42 vs. 66.80±9.61 ($P<0.001$) at 72 hours (Figure 2).

CONCLUSION Whole-body radioiodine retention 72 hours after ^{131}I therapy is paradoxically higher in patients treated with furosemide and potassium chloride, being 1.6-fold greater than that in the control group. The authors do not recommend furosemide as an adjunct therapy for ^{131}I ablation in patients who have been iodine-depleted by a low-iodine diet. The authors concluded that whether iodine depletion is the cause of the paradoxical effect remains uncertain.

COMMENTARY

This study was designed to explore whether furosemide would accelerate the renal excretion of unbound urinary iodine, and whether this would decrease the adverse effects of ^{131}I and shorten the hospital stay of patients. Just the opposite was observed. Urinary ^{131}I excretion was significantly lower in patients who were taking furosemide, and their blood radioactivity levels were almost threefold those in patients not taking the diuretic. The authors concluded that the exact mechanism for this paradoxical effect of furosemide is unclear and should be studied further.

A few studies found that the administration of diuretics can improve ^{131}I clearance, reducing radiation burden and shortening of hospital stay. For example, Seabold et al. found that the mean half-time of ^{131}I renal clearance for the patients treated with furosemide decreased by 12 hours ($P<0.05$) but was not significantly decreased for those who received thiazides (1). However, another study by Tepmongkol et al. (2) found that hydrochlorothiazide significantly improved 24-hour ^{131}I uptake in patients with a normal iodide pool, as compared with patients who were on a low-iodine diet.

In another study, Maruca et al. (3) tested the efficacy of iodine depletion and diuretics as a means of enhancing ^{131}I uptake by DTC metastases. Total-body iodine decreased about 65%, and the amount of ^{131}I taken up and retained by tumor increased almost 150%; however, ^{131}I renal clearance decreased by 56% and total-body radiation from 150 mCi increased almost 70%. As a consequence, the authors concluded that iodine-depletion regimens are less effective than prior studies have suggested. Still, it is difficult to compare studies of the effects of diuretics on ^{131}I retention, because the study protocols were so different.

Of considerable importance, all of the previous studies, including that by Matovic et al., used thyroid hormone withdrawal to prepare patients for ^{131}I therapy, and as a consequence, hypothyroidism that almost certainly diminished renal clearance developed in all of the patients. This is a major issue.

Using recombinant human TSH (rhTSH) provides insight about excretion rates of ^{131}I in patients pretreated with rhTSH as compared with thyroid hormone withdrawal. In 2006, Pacini et al. (4) first found that whole-body radiation was approximately one-third lower with rhTSH preparation for remnant ablation with 100 mCi of ^{131}I as compared with thyroid hormone withdrawal. This observation subsequently sparked further study.

Hanscheid et al. (5) found that the effective half-time of ^{131}I in the thyroid remnant was nearly 1.5-fold greater after rhTSH than after thyroid hormone withdrawal ($P = 0.01$), whereas the mean 48-hr ^{131}I thyroid uptakes were not significantly different between the rhTSH and thyroid hormone withdrawal. The maximum mean absorbed dose of ^{131}I to the blood was almost 2-fold greater with thyroid hormone withdrawal than with rhTSH ($P <0.0001$), indicating that higher activities of radioiodine might be safely administered after exogenous stimulation with rhTSH.

A more recent study by Remy et al. (6) found the mean effective total-body ^{131}I half-life (10.5 hr) was significantly shorter (31%) among patients pretreated with rhTSH as compared with patients who underwent thyroid hormone withdrawal (15.7 hr). This is thus a 31% reduction in total-body radiation in patients pretreated with rhTSH. The ^{131}I residence times in the stomach and in the rest of the body were significantly shorter in patients who received rhTSH as compared with those who underwent thyroid hormone withdrawal, but the residence times were similar in the colon and bladder. The difference in total-body ^{131}I retention was correlated with renal function: patients who had thyroid hormone withdrawal had a longer mean effective ^{131}I half-life that was mainly due to delayed renal excretion of ^{131}I.

There is little doubt that the most important feature of ^{131}I therapy is the extent to which the isotope is concentrated by thyroid tumors and normal tissues throughout the body. Retention of ^{131}I in these tissues is a two-edged sword. With malignant tumors, the goal is to increase retention time of the isotope in tumor cells, thus increasing the ^{131}I effective half-life without exerting this effect in normal tissues. Still, with

normal tissues such as the salivary glands, lacrimal ducts, stomach, and breast tissues—all of which contain sodium iodide symporters—the prolonged half-life of ^{131}I in the body is injurious to normal tissues and potentially produces second malignancies years after the isotope has been administered.

There are other ways to influence the effective half-life of ^{131}I in thyroid tumor cells, such as using low-iodine diets and administering lithium prior to ^{131}I therapy (7). Yet the most widely used method that has been used for decades is to manipulate serum TSH concentrations by withdrawing thyroid hormone, paradoxically decreasing the effective half-life of ^{131}I in tumor tissue and increasing the whole-body retention of ^{131}I in normal tissues. The most sensible approach is to perform remnant ablation with rhTSH preparation and to use the smallest possible amount of ^{131}I to achieve remnant ablation, which is somewhere between 30 (8) and 50 mCi (9).

It seems probable that the findings by Matovic et al. reflect the physiologic changes related to thyroid hormone withdrawal that produces overt hypothyroidism, which significantly reduces renal clearance of ^{131}I. The outcome of this study likely would have been much different had rhTSH been used to decrease the duration of hospitalization and to decrease whole-body retention of ^{131}I.

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Lymph-node metastases and TNM stage portend unfavorable prognosis in patients with well-differentiated thyroid microcarcinoma of various histologies

Tzvetov G, Hirsch D, Shraga-Slutzky I, Weinstein R, Manistersky Y, Kalmanovich R, Lapidot M, Grozinsky-Glasberg S, Singer J, Sulkes J, Shimon I, Benbassat C. Well-differentiated thyroid carcinoma: comparison of microscopic and macroscopic disease. Thyroid 2009;19:487-94.

SUMMARY

BACKGROUND The incidence of thyroid cancer has been gradually increasing over the past three decades, especially that of papillary thyroid cancers ranging in size from <1 to 2 cm. As a consequence, this has produced a diverse range of opinions concerning the management of this low-risk group of cancers. This is a retrospective study that compares the outcomes of well-differentiated microscopic and macroscopic nonmedullary thyroid cancers of follicular-cell origin.

METHODS This is a retrospective study of patients treated for thyroid cancer in the Rabin Medical Center in Israel from 1973 through 2005, when a thyroid cancer tumor registry was established. The study subjects comprised 768 of 1030 patients (75%) with well-differentiated thyroid cancer (DTC) for whom the registry data were complete (Here and elsewhere, percentages >1% are rounded to the integer.) Of the 768 patients with DTC, 543 had macroscopic tumors (71%) and 225 had microscopic tumors (29%). The remaining patients were excluded from this study because of incomplete data. Microscopic DTC was defined as a tumor ≤1 cm, regardless of the circumstances in which the tumor was identified, and as macroscopic if the tumor was >1 cm. Most patients were treated with total thyroidectomy, although 10 with microscopic tumors (1%) and 13 with macroscopic tumors (2%) were included in the total thyroidectomy group. Lymph-node metastases were treated with neck dissection, the extent of which was not further defined. Follow-up studies were performed with serum thyroglobulin (Tg), neck ultrasonography, and diagnostic whole-body radioactive iodine (^{131}I) scans (DxWBS), which were performed either periodically or on an as-needed basis.

The tumor registry established in 2005 provided data on patient age, sex, tumor histopathology, and primary therapy and the extent of tumor, local recurrence, and distant metastases. In some cases, however, the original diagnoses dated back as far as 1970 and were not available for review. Tumor was regarded as intrathyroidal if vascular invasion or tumor extension remained within the thyroid margins. Tumor multifocality was defined as

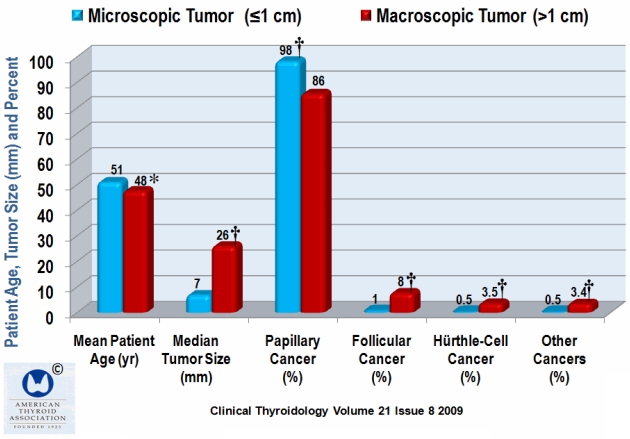

Figure 2. This figure shows mean patient age, median tumor size, and tumor histology. *P<0.01 and †P <0.001, comparing microscopic and macroscopic tumors. Derived from data in Table 1 of Tzvetov et al.

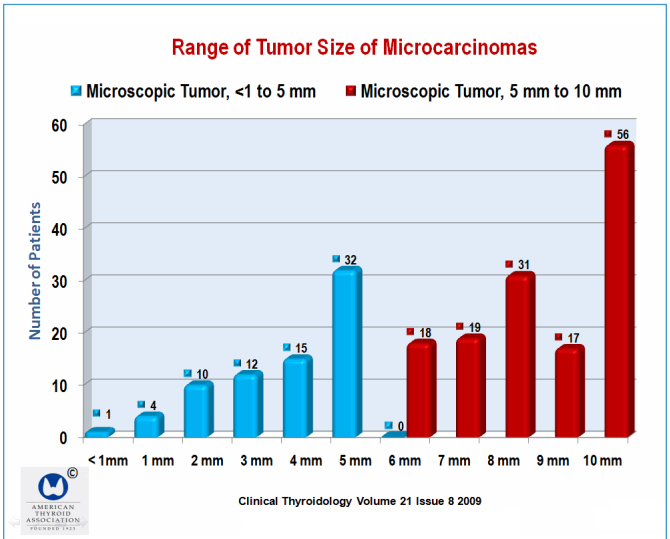

Figure 1. This figure shows the range of microcarcinomas in this study. Adapted from Figure 1 in Tzvetov et al.

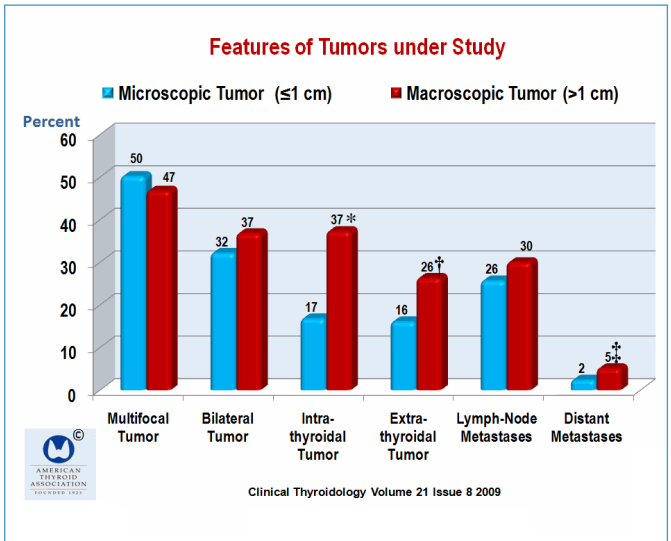

Figure 3. This figure shows the features of the tumors in this study. *P<0.01. †P = 0.02. ‡P = 0.16. Derived from Table 1 in Tzvetov et al.

more than one tumor in one or both thyroid lobes. Persistent or recurrent disease was defined as detectable tumor 1 year after initial therapy, which included surgery with or without ^{131}I therapy. Tumor was identified by neck ultrasonography, cytologic findings, elevated serum Tg levels, or ^{131}I uptake outside the thyroid bed. Persistent or recurrent tumors were grouped together as recurrent disease. Patients were considered free of disease if they had undetectable TSH-stimulated serum Tg levels, negative neck ultrasonography and a negative DxWBS at the last follow-up study. Staging was performed according to the 6th edition of the TNM (tumor–node–metastasis) staging system.

RESULTS Of the patients with DTC, 225 (29%) had microscopic and 543 (71%) had macroscopic tumors. The range of microscopic tumor size is shown in Figure 1. Hemithyroidectomy was performed in 12 patients (2%) versus 52 patients (23%), in the microscopic and macroscopic groups, and neck dissection was performed in 43 (19%) versus 98 (18%) (P not significant [NS]). The median ^{131}I activity that was administered initially was 100 mCi (range, 30 to 250) versus 150 mCi (range, 30 to 250).

At the time of initial treatment, the mean (±SD) patient age was 51±14 versus 47.5±16.1 years (P<0.01) and the mean tumor size was 6.8±2.7 versus 25.9±13.5 mm for patients with microscopic and macroscopic tumor. Of the microscopic cancers, 221 were papillary (98%), 2 were follicular (0.9%), 1 was a Hürthle-cell cancer (0.05%), and 1 was reported as "other cancer" (3.4%). Of patients with macroscopic tumors, 464 of 543 (86%) had papillary, 41 follicular (8%), 19 Hürthle-cell (4%), and 18 (3%) other cancer (P<0.001 for microscopic vs. macroscopic tumors for each of the 4 histologic types reported) (Figure 2). Multifocal tumor was found in 108 (50%) versus 241 (47%) patients, with microscopic and macroscopic tumor (P = NS); bilateral tumor was found in 69 (32%) versus 187 (37%) (P = NS). Intrathyroidal tumor was found in 35 (17%) versus 176 (37%) of the microscopic and macroscopic tumors (P<0.001), extrathyroidal extension in 36 (16%) vs. 131 (26%) (P = 0.02), lymph-node metastases in 55 (26%) versus 154 (30%) (P = NS), and distant metastases in 5 of 208 (2%) versus 26 of 508 (5%) (P = 0.016) (Figure 3). The TNM stage was I in 139 (74%) versus 269 patients (63%) (P = 0.04), stage II in 1 (0.5%) versus 51 patients (12%) (P = 0.02), stage III in 33 (18%) versus 59 (14%) (P = NS), and stage IV in 15 (8%) versus 45 (11%), with microscopic and macroscopic tumors (P = NS) (Figure 4).

The median duration of follow-up was 5 years in both groups. Tumor recurrence was found in 20 of 182 patients (11%) versus

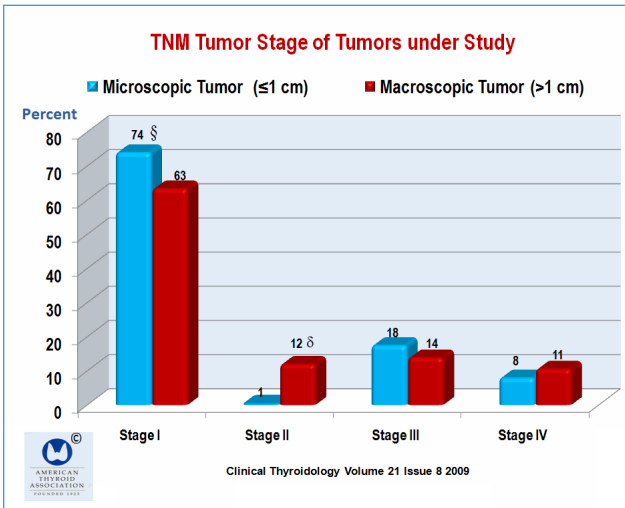

Figure 4. TNM tumor stages in this study. †P <0.001, comparing microscopic and macroscopic tumors. §P = 0.04 and δP<0.02, comparing microscopic and macroscopic tumors. Derived from data in Table 2 of Tzvetov et al. Stage III and IV were not significantly different in the microscopic and macroscopic tumor groups.

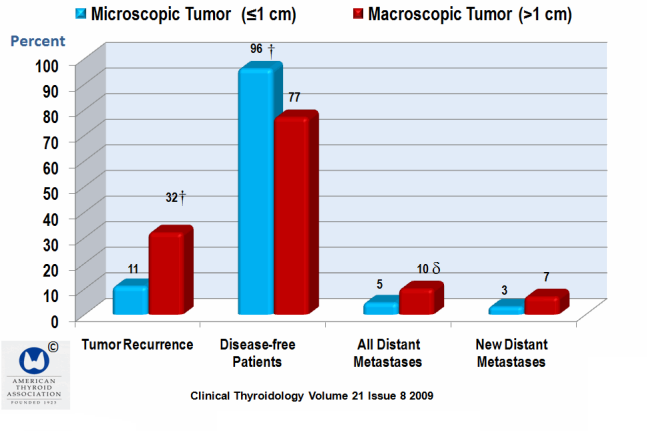

Figure 5. This figure shows overall rates of tumor recurrence, disease-free outcomes, all distant metastases, and new distant metastases. †P <0.001. δP < 0.02. Adapted from Figure 2 of Tzvetov et al. There were no significant differences in the rates of new distant metastases in the two groups.

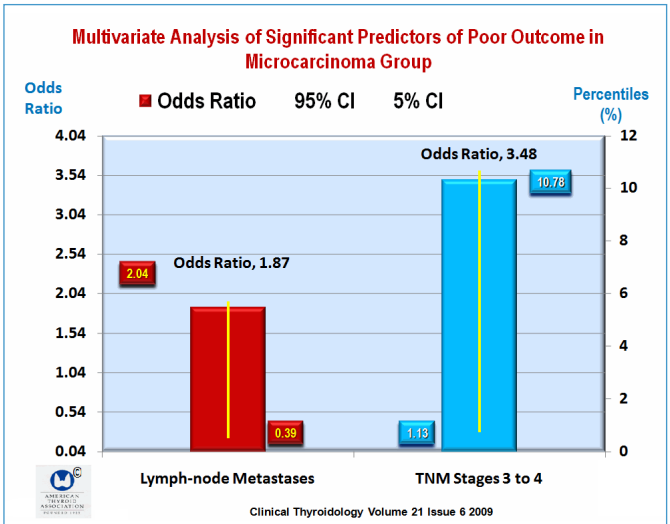

Figure 6. Multivariate analysis found only two parameters that were significant predictors of an adverse outcome in the microcarcinoma group: lymph-node metastases (OR, 1.87; 95% confidence interval [CI], 2.04 to 0.39) and TNM stages III to IV (OR, 3.48, 95% CI, 1.13 to 10.74). Also, lymph-node metastasis at initial diagnosis was correlated with young age (P = 0.001), male sex (P = 0.03), and tumor multifocality (P = 0.001).

151 of 474 (32%) patients with microscopic and macroscopic tumors, (P<0.001); overall, distant metastases were found in 10 of 225 patients with microscopic disease (5%) versus 54 of 543 patients (10%) with macroscopic disease (P = 0.02). New distant metastases were found in 5 patients with microcarcinomas; 5 were in the lung, 3 were in bone, and for 1 patient each tumor was in the liver and skin, as compared with 31 in the lung, 5 in the bone, 2 in the brain, and 1 in the adrenal gland in patients with macroscopic tumors. At the end of follow-up, 216 patients (96%) in the microscopic and 543 (77%) in the macroscopic tumor group were disease-free (P<0.001) (Figure 5). Of 10 patients with distant metastases who initially had microscopic tumors, 6 had classic papillary thyroid cancer or follicular variant papillary cancer. The site of distant metastases in this group was the lung with or without bone metastases; the other 4 had lung metastases from follicular thyroid cancer, which in some cases also involved bone, liver, or skin.

Univariate analysis found that lymph-node metastases and distant metastases were the only two variables associated with an unfavorable outcome in patients with microcarcinomas. On multivariate analysis using stepwise logistic regression, the only two tumor features found to be significant predictors of a poor outcome were lymph-node metastases (odds ratio [OR], 1.87; 95% confidence interval [CI]2.04 to 0.39,) (Figure 6), and TNM stages III to IV (OR, 3.48; 95% CI, 1.13 to 10.74) (Figure 6). Lymph-node metastases at the time of initial diagnosis were correlated with younger age (P = 0.001), male sex (P = 0.03), and tumor multifocality (P = 0.001). Distant metastases and ^{131}I therapy were excluded from the model because both were highly correlated with outcome.

CONCLUSION Lymph-node metastases and TNM stage independently portend an unfavorable prognosis in patients with well-differentiated thyroid microcarcinoma of various histologies.

COMMENTARY

Although the steady increase in thyroid cancers smaller than 2 cm is generally regarded to be a result of the widespread use of neck ultrasonography, there is reason to believe that this only partially accounts for this phenomenon, which has occurred around much of the world. The most widely quoted recent article on this subject is a study of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database by Davies and Welch (1), who concluded that the increasing incidence of thyroid cancer in the United states is predominantly due to the increased detection of small papillary cancers by neck ultrasonography. They suggest that the growing incidence of thyroid cancer reflects an increased detection of subclinical disease, not an increase in the true occurrence of thyroid cancer. This article sparked several other similar studies.

An important study of the SEER database by Enewold et al. (2) concluded that medical surveillance and more sensitive diagnostic procedures cannot entirely account for the observed increases in papillary thyroid cancer rates, pointing out that among white women the rate of increase for papillary thyroid cancers >5 cm almost equaled that for the smallest cancers ≤1 cm. The authors suggested that other possible explanations for this phenomenon should be explored.

A more recent study of the SEER database by Chen et al. (3) found that the incidence rates of differentiated thyroid cancers of all sizes increased between 1988 and 2005 in both men and women. They found that the increased incidence rates across all tumor sizes suggests that increased diagnostic scrutiny is not the entire explanation for the increased rate of thyroid cancer in the past three decades. The authors concluded that other explanations, including environmental influences and molecular pathways, should be investigated.

A recent study from northwestern Spain (4) also found that the incidence of thyroid cancer has been increasing. The study found that this may reflect a contribution of other factors in addition to increased diagnostic activity, which may have contributed to the rising incidence of thyroid cancer in northwestern Spain. The authors suggested that additional studies are needed to explain this phenomenon, as there may be other unrecognized risk factors causing this problem.

Tzvetov et al. also suggest that ultrasound surveillance may account for the increased incidence of small thyroid cancers, although the study does not directly address this issue. The study compares the clinical course of well-differentiated microscopic thyroid cancers ≤1 cm with that of macroscopic tumors larger than 1 cm. Several aspects of this study bear close scrutiny. The patients with microscopic tumors were significantly older than those with macroscopic tumors, and the initial treatment was not uniform in the two groups. Total or subtotal thyroidectomy was performed in 98% of the patients with tumors larger than 1 cm, as compared with 77% of the patients with microcarcinomas. Also, ^{131}I was given to 16% of the patients with microcarcinomas and 23% of those with macrocarcinomas.

Tzvetov et al. conclude that the differences among patients with microscopic DTC and those with macroscopic tumors may not justify a different therapeutic approach. However, there are data suggesting otherwise. Six articles were cited by Tzvetov et al., that showed recurrence rates ranging from 11% to as low as 1.7% in studies by other authors, including Roti et al. (5), Chow et al. (6) , Ito et al. (7), Noguchi et al(8). and Hay et al. (9). Perhaps the most extensive study concerning this issue is that by Bilimoria et al. (10), in which a total of 52,173 patients with papillary thyroid cancer were studied, and for whom the 10-year tumor recurrence rate was approximately 5% for tumors smaller than 1 cm and 7% for tumors 1 to 1.9 cm. Moreover, the 10-year cancer-specific mortality rate was 2% for papillary microcarcinomas <1 cm and almost 3% for tumors 1 to 1.9 cm. Yet among a subset of 15,547 patients with papillary thyroid cancers ranging from 1 to 2 cm, those with lobectomy experienced a 24% higher risk for recurrence (P = 0.04) and a 49% higher 10-year thyroid cancer mortality rate as compared with patients who were treated with total thyroidectomy. The study also found that there was no significant difference in recurrence or survival rates between lobectomy and total thyroidectomy for patients with papillary thyroid cancers <1 cm in diameter. This conclusion parallels the recent recommendation made in the ATA guidelines for the management of papillary thyroid cancer.

— Ernest L. Mazzaferri, MD, MACP

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DISCLOSURE

Dr. Mazzaferri receives honorari from Genzyme for providing lectures,

Dr. Sipos receives honoraria from Abbott and Genzyme for providing lectures.

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