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SUMMARY

BACKGROUND
Adequate dietary iodine intake is required for thyroid hormone synthesis. The iodine nutritional status of the U.S. population has been assessed periodically since 1971 by the National Health and Nutritional Examination Survey (NHANES). The recommended dietary allowances for iodine are 150 µg daily in nonpregnant adults and 220 µg daily in pregnant women. Major sources of iodine in the U.S. diet include iodized salt, dairy foods, and some grain products. Because 90% of ingested iodine is excreted in the urine, median urinary iodine concentrations can be used to assess the dietary iodine status of populations. The World Health Organization has determined that a median urinary iodine level of 100 to 199 µg/L reflects optimal iodine nutrition for populations of nonpregnant adults. During pregnancy, because dietary iodine requirements and renal iodine excretion are both increased, a median urinary iodine concentration of 150 to 249 µg/L is considered optimal.

METHODS
Spot urinary iodine measurements were obtained in about one third of the 5000 participants in the 2005–2006 NHANES and in all of the 5000 participants 6 years of age or older in the 2007–2008 NHANES. Sampling was designed to be nationally representative. Subjects were categorized by age group, sex, and race/ethnicity. Pregnant women were identified on the basis of urine testing.

RESULTS
Overall population median urinary iodine concentrations were 164 µg/L (95% CI, 154 to 174) in 2005–2006 and 164 µg/L (95% CI, 154 to 173) in 2007–2008. These values have not changed substantially in NHANES surveys since 2000. Children had higher urinary iodine concentrations than adults; the median urinary iodine concentration for children 6 to 11 years of age was 239 µg/L (95% CI, 193 to 279) in 2005–2006 and 215 µg/L (95% CI, 194 to 240) in 2007–2008.

U. S. DIETARY IODINE STATUS REMAINS SUFFICIENT OVERALL, BUT WOMEN OF CHILD-BEARING AGE MAY BE MILDLY IODINE-DEFICIENT


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Non-Hispanic black individuals had lower urinary iodine concentrations (2007–2008 median urinary iodine concentration, 137 µg/L; 95% CI, 123 to 155) than non-Hispanic white individuals (2007–2008 median urinary iodine concentration, 168 µg/L; 95% CI, 154 to 180) and Mexican Americans (2007–2008 median urinary iodine concentration, 174 µg/L; 95% CI, 162 to 190).

In the combined dataset from 2005–2006 and 2007–2008 there were a total of 184 pregnant women. Their median urinary iodine concentration was 125 µg/L (95% CI, 86 to 198). The combined dataset also included 1578 nonpregnant women of child-bearing age (15 to 44 years); the median urinary iodine concentration for this group was 130 µg/L (95% CI, 116 to 139).

**CONCLUSIONS**

Iodine nutrition in the United States remains adequate overall, and U.S. dietary iodine intake has remained stable since 2000. However, children may be ingesting slightly excessive amounts of iodine, and pregnant U.S. women are mildly iodine-deficient.

**COMMENTARY**

The 2007–2008 NHANES survey is the first in which urinary iodine values were measured in all participants, and it represents the largest dietary iodine assessment in the United States to date. In light of the 50% drop in urinary iodine values between NHANES I (1971–1974) and NHANES III (1988–1994) (1), it is reassuring that U.S. urinary iodine values have since stabilized and that overall U.S. iodine intake is adequate.

However, the fact that pregnant women in the samples from 2005–2006 and 2007–2008 were mildly iodine-deficient is quite worrisome. Because thyroid hormone is essential for normal neurodevelopment in utero and in early life, the groups most vulnerable to the effects of iodine deficiency are pregnant and lactating women and their offspring. Decreases in maternal and fetal free T4 associated with even mild iodine deficiency in pregnancy may have adverse effects on cognitive function in children (2,3). While larger than in previous NHANES datasets, the sample size of 184 is far too small to be truly representative of all pregnant U.S. women. More information is needed about risk factors for low dietary iodine intake among pregnant U.S. women. Data about regional and racial/ethnic variations in urinary iodine concentrations would be useful in this regard. To achieve a sample size adequate to allow for more subgroup analyses, oversampling of pregnant women should be carried out during the next NHANES survey. Until we are better able to identify particular U.S. women at risk for iodine deficiency, all pregnant and lactating women in the United States are best advised to take a prenatal multivitamin containing 150 µg of iodine daily (4).

In all of the NHANES surveys to date, children have had higher median urinary iodine concentrations than adults. This is most likely explained by children’s higher dairy intakes. Whether the marginally excessive iodine intake among U.S. children will predispose them to higher rates of thyroid autoimmunity and/or thyroid dysfunction later in life is unknown. More studies are needed to better understand the effects of different levels of iodine ingestion throughout the life cycle.

— Elizabeth N. Pearce, MD, Boston, Massachusetts

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REFERENCES


**SODIUM SELENITE IMPROVES MILD GRAVES’ EYE DISEASE**


**SUMMARY**

**BACKGROUND**
Mild Graves’ orbitopathy (GO) reduces quality of life. The condition improves spontaneously in one fifth of patients, remains static in two thirds, and progresses in the remainder. Cytokines and oxygen free radicals in the orbit may be pathogenic for GO. When it is severe, GO is treated with corticosteroids or decompressive surgery. Selenium is thought to be beneficial for Hashimoto’s thyroiditis. Pentoxifylline is a phosphodiesterase inhibitor that also has anti-inflammatory and immunomodulatory effects. The purpose of this study was to evaluate these two agents in the treatment of mild GO.

**METHODS**
This was a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 159 patients. Patients were randomly assigned to receive placebo, selenium as sodium selenite (not “selenium selenite”) 100 µg twice daily, or pentoxifylline 600 mg twice daily in capsules that appeared identical, for a total of 6 months. Patients were evaluated at baseline, 3, 6, and 12 months by an ophthalmologist who determined a clinical activity score that evaluated seven items. They also were given a quality of life Graves’ orbitopathy questionnaire (GO-QOL). The primary end points were the ophthalmologic assessment and GO-QOL score at 6 months.

**RESULTS**
The mean age of the patients was 43 to 44 years. About two thirds of them were treated with antithyroid drugs during the study; the remainder were euthyroid while taking levothyroxine after thyroidectomy or radiiodine treatment. A total of 35% to 50% were current smokers. The GO-QOL score for visual function improved in 62% and the appearance improved in 75% of the selenium group; the magnitude of the improvement was much better than in the other groups. The overall ophthalmic outcome at 6 months was much better in the selenium group than in the other groups and the rate of worsening was less in the selenium group. The beneficial effect of selenium persisted for 6 months after therapy. The eyelid aperture improved in 37% of the selenium group but in only 12% of the placebo group and 15% of the pentoxifylline group. Drug-related adverse events occurred in seven patients taking pentoxifylline but did not occur in the other groups.

**CONCLUSIONS**
Treatment with selenium significantly improved quality of life and reduced ocular involvement and slowed its progression in patients with mild Graves’ orbitopathy.

**COMMENTARY**
Management of hyperthyroidism is straightforward and successful in patients with Graves’ disease, but management of the eye condition is problematic because there is no simple effective therapy. In my experience, the eye condition may cause considerable concern, especially in young women, and thus it poses a vexing problem. This multicenter study has produced a remarkable therapeutic result by showing that sodium selenite clearly improves Graves’ eye disease in a majority of patients, with virtually no side effects. Although these patients did not have severe ophthalmopathy that may have required corticosteroids, radiation, or surgery, they were clearly troubled by their appearance. The mechanism of the effect is unclear; the authors speculated that selenium reduced reactive oxygen species.

To place the selenium dose in perspective, it should be noted that the National Institutes of Health Office continued on next page
SODIUM SELENITE IMPROVES MILD GRAVES’ EYE DISEASE

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of Dietary Supplements recommends a selenium intake of 55 µg per day, presumably in food. The maximum safe selenium intake is estimated to be 600 µg per day (1).

One concern about adoption of this therapy is that the study was relatively small. There were only 54 patients in the selenium group, but they did much better than the 50 in the placebo group or the 48 in the pentoxifylline group. Because this therapy is inexpensive and apparently harmless, I am tempted to use it in my treatment of patients with Graves’ disease who have any degree of clinical eye involvement. A sodium selenite capsule containing 100 µg of selenium costs only 10 cents (Internet price). Let’s hope that a drug company does not get an FDA approval for selenium for Graves’ eye disease and then sell it for $10 per capsule.

— Jerome M. Hershman, MD

Reference
OPTIMIZING THE DOSE OF $^{131}$I CURES HYPERTHYROIDISM WITHOUT CAUSING HYPOTHYROIDISM


SUMMARY

BACKGROUND

In China, the prevalence of hyperthyroidism is 3%; 90% of these cases are due to Graves’ disease. Treatment with radioactive iodine ($^{131}$I) for Graves’ disease is becoming increasingly common in China. In the rural areas where most of the population reside, lifelong treatment with levothyroxine is difficult. The purpose of this study was to optimize the dose of $^{131}$I in order to achieve a cure of the hyperthyroidism with a low rate of hypothyroidism.

METHODS

This is a 12-year prospective, randomized study. Six hundred patients who had Graves’ disease and were older than 8 years of age participated. They were newly diagnosed patients on antithyroid drugs (ATDs) or those who had a history of taking the drugs; thyroid tests indicated hyperthyroidism, and thyroid uptake had to be greater than 40% while not taking antithyroid drugs. The patients were randomly assigned to one of five groups that received activities of 0.37, 1.11, 1.85, 2.56, and 3.33 MBq per gram of thyroid tissue adjusted for the 24-hour thyroid uptake (1 MBq = 0.027 mCi). However, the dose was also adjusted based on a scoring system for six clinical factors. Scores were rated as 0, 1, or 2 for the following factors: gland texture (soft, moderate, or hard), course of disease (<6 months, 6 months to 2 years, and >2 years), previous ATD (none, <2 years, or >2 years), state of disease (mild, moderate, or severe), complications (none, moderate, or severe), and age (<14 years, 14 to 18 years, and >18 years). Total scores ranged from 0 to 12, with an increase of 0.37 MBq per score of 2. Gland weight was estimated by ultrasound.

After the administration of $^{131}$I, patients received propranolol, if necessary, and ATD, which was withdrawn 3 days before the follow-up visit.

RESULTS

A total of 529 patients completed the study. The mean age was approximately 35 years, three fourths were women, the mean gland weight was about 60 g, and the mean 24-hour uptake was about 65%. The optimal result was achieved in group 3. Based on the clinical factors, the dose was increased from 1.85 to 2.61 MBq/g with a broad range of 37 to 833 MBq/g. The mean (±SD) dose for the group was 261±162 MBq (7.05±4.39 mCi). In this group, 72% maintained a euthyroid state, 6% remained hyperthyroid, and 22% became hypothyroid, but 14% had recurrences during the 12-year follow-up.

CONCLUSIONS

The treatment protocol was effective for treating hyperthyroidism with a relatively low rate of hypothyroidism in the 12-year follow-up.

COMMENTARY

Many years ago, attempts were made to provide exactly the right dose of $^{131}$I to cure hyperthyroidism without causing hypothyroidism or requiring repeated doses of $^{131}$I. Because cure without the complication of hypothyroidism was so infrequent, the recent approach has been to give a relatively large dose within the range of 100 to 200 µCi/g thyroid corrected for the 24-hour thyroid uptake (1). Some nuclear medicine units use arbitrary doses of 10 to 15 mCi, while others aim for 160 µCi/g. With this approach, the treatment has been called “ablation,” because hypothyroidism is so often the outcome. I have nearly given up on correcting our fellows and...
residents who call radioiodine treatment of Graves’ hyperthyroidism “thyroid ablation” rather than “treatment”; ablation implies that hypothyroidism is inevitable, whereas “treatment” leaves the possibility that there may be an outcome of euthyroidism.

The clinical features used for optimizing the dose in the current study may be somewhat arbitrary, such as determining the texture of the gland or the duration of the disease. Nevertheless, within the 12 years of follow-up, the results are impressive. Unfortunately, the history of radioiodine therapy in the United States and Europe makes me suspect that the good outcome will not persist as the patients are followed longer. Sridama et al. at the University of Chicago tried a low-dose program to cure hyperthyroidism many years ago and still found that the incidence of hypothyroidism at 12 years of follow-up was 73% (2). Many other reports showed that the incidence of hypothyroidism tended to increase at a rate of 2% to 4% per year after 10 years, leading to the conclusion that hypothyroidism eventually develops in nearly all patients after ¹³¹I therapy for Graves’ disease. However, my personal experience shows otherwise. Some patients are euthyroid in long-term follow-up.

However, a study of 1086 patients with Graves’ disease treated with ¹³¹I in Finland using a dose similar to that used in group 3 of the study under discussion, 7 mCi, found an incidence of 59% hypothyroidism at 10 years and 82% at 25 years (3). Perhaps paying attention to the clinical factors cited in the study under discussion will improve this result. I am optimistic.

— Jerome M. Hershman, MD

References

PRECONCEPTION L-T_4 TREATMENT IS BENEFICIAL IN SUBFERTILE WOMEN WITH SUBCLINICAL HYPOTHYROIDISM UNDERGOING IN VITRO FERTILIZATION TREATMENT


SUMMARY

BACKGROUND
Pregnant women with hypothyroidism are at increased risk of antepartum obstetric complications, mainly miscarriages and premature deliveries. Whether therapy of fertility is affected by autoimmune thyroid disease (ATD) is debatable. The incidence of miscarriages after in vitro fertilization (IVF) in women with ATD appears to be increased. The objective of the authors was to investigate whether levothyroxine (L-T_4) treatment has beneficial effects on the results of IVF and the outcome of pregnancy in infertile patients with subclinical hypothyroidism who are undergoing IVF/intracytoplasmic sperm injection (ICSI).

METHODS
This is a prospective, randomized trial at a university-affiliated infertility clinic in Seoul, South Korea. All subjects had regular ovulatory cycles (duration, 21 to 35 days). They were in good health, with normal cardiac, hepatic, and renal functions, and they had experienced spontaneous onset of puberty and normal sexual development. None had a history of subclinical or clinical hypothyroidism, and they had not taken any infertility medications (clomiphene and/or gonadotropins) within the preceding 3 months.

A total of 64 infertile patients with subclinical hypothyroidism (serum thyrotropin [TSH] level, >4.5 mIU/L, with a normal serum free thyroxine [T_4]) were recruited. Patients were randomly assigned to an L-T_4 treatment group (mean TSH [±SD], 6.6±1.7; 95% confidence interval [CI], 4.6 to 9.8; free T_4, 1.2±0.2) or a control group (TSH, 6.7±1.8; 95% CI, 4.6 to 9.6; T_4, 1.2±0.2) (P not significant). There were no differences in patient characteristics between the two groups; the mean age was 36.0±2.4 years in the L-T_4 treated women, as compared with 36.1±2.2 in the controls (P not significant). The indications for IVF were not significantly different among the two groups: tubal factor, 31.1% versus 28.1%; endometriosis, 18.7% versus 21.9%; male factor, 40.6% versus 40.6%; and unexplained, 9.4% versus 9.4%. For the L-T_4 treatment group, 50 µg of L-T_4 was administered from the first day of controlled ovarian stimulation for IVF/ICSI, and it was continued up to the day of serum b-human chorionic gonadotropin measurement, at which time, serum TSH, free T_4, thyroid peroxidase autoantibody (TPOAb) and thyroglobulin antibody (TGAb) were also measured (L-T_4 treatment group TSH, 2.3±0.4, vs. control group TSH 6.9±2.0; P<0.001; free T_4, 1.4±0.3 vs. 1.0±0.2; P<0.001). If pregnancy was confirmed, an adequate dose of L-T_4 was given continuously throughout the pregnancy. Even in pregnant women included in the control group, an adequate dose of L-T_4 was supplemented when overt hypothyroidism was detected during pregnancy. The L-T_4 dosage was titrated to reach and thereafter maintain serum TSH concentrations of <2.5 mIU/L in the first trimester. Serum TSH and free T_4 levels were remeasured every 4 to 6 weeks.

RESULTS
Total dose and days of recombinant human FSH used for controlled ovarian stimulation were similar among the two groups. The number of grade I or II embryos was significantly higher in the L-T_4 treatment group than in the control group. There was no significant difference in the clinical pregnancy rate per cycle between the two groups (17 of 32 [53.1%] in the treatment groups vs. 12 of 32 [37.5%] in the controls; P not significant). However, the miscarriage rate was significantly lower in the L-T_4 treatment group than in the control group (P = 0.021), as well as the live birth

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rate per cycle initiated (53.1% vs. 25%; P = 0.039). In the control group, both TPOAb and TGAb levels were significantly higher in the subgroup with miscarriages than in the subgroup with deliveries. One woman in the control group had overt hypothyroidism at 24 weeks of gestation. Prematurity at 31 weeks of gestation occurred in one woman in the control group; no prematurity occurred in the treated group.

**CONCLUSIONS**

L-T4 treatment can improve embryo quality, implantation rate, and live birth rate in infertile women with subclinical hypothyroidism undergoing IVF/ICSI. The dose of L-T4 should be adjusted as the pregnancy progresses.

**COMMENTARY**

Abnormal obstetrical outcomes, mainly miscarriages and preterm delivery in women with autoimmune thyroid disease, have recently been established in two meta-analysis publications (1, 2). In some, but not all, of the studies, serum TSH values were above the accepted normal range for the first trimester of pregnancy (3), implying the possibility of subclinical hypothyroidism as an additional risk factor for obstetrical complications. In one of the meta-analyses (2), the incidence of miscarriages in subfertile women with chronic thyroiditis (eight publications with a total of 233 TPOAb-positive women) was significantly higher as compared with women with negative thyroid autoantibodies (1758 women; odds ratio, 3.15; 95% CI, 2.23 to 4.44. In the only previous prospective study of 24 euthyroid TPOAb-positive women who were undergoing assisted fertility treatment and given L-T4, the miscarriage rate was not statistically different from that in the control group (4). One important unique feature of the protocol in the study under discussion is that L-T4 treatment of subclinical hypothyroidism was started at the beginning of IVF treatment, with normalization of serum TSH in the majority of patients at the time of implantation and the adjustment of L-T4 dosage with progression of pregnancy. Whether the beneficial effect of L-T4 treatment is due to embryo quality, implantation, or both is unclear at present. The importance of assessing thyroid function in women undergoing fertility treatment appears reasonable in view of this study. Contrary to the authors’ statement that “thyroid evaluation has become a routine workup for infertile women,” it is my experience in clinical practice that thyroid tests are not performed routinely before IVF treatment, even on women who are receiving L-T4 treatment.

— Jorge H. Mestman, MD

**References**


**SUMMARY**

**BACKGROUND**
The most characteristic clinical hallmark of a malignant thyroid nodule is its rapid growth. However, even benign thyroid nodules may attain a considerable size within a short period. Fine-needle aspiration cytology (FNAC) and ultrasonography are the most widely used techniques to distinguish malignant from benign nodules. Much effort has been invested in unraveling the molecular signaling pathways that may help promote malignant growth, but only a few studies are available on the mechanisms that enhance the growth rate of benign nodules, particularly the so-called cold nodules.

In thyroid cancers, one of the known growth-promoting factors is a constitutive activation of chimeric cytoplasmic kinases that result from a rearrangement of the RET/PTC genes. This rearrangement is by itself not a marker for malignancy, since it also occurs in benign nodules. The authors performed a prospective multicenter study to determine whether the RET/PTC rearrangement may be a mechanism that promotes the growth of a particular subset of benign nodules.

**METHODS**
A total of 125 patients were included in this Italian study. One of the inclusion criteria was a nodular diameter of 10 mm or more, the other being the results of FNAC, which were required to be consistent with a Thy2 colloid nodule (according to the criteria of the British Thyroid Association). When more than one nodule was present, only the largest one was considered. The size of the nodules was measured by ultrasonography. Patients on suppressive thyrotropin therapy and/or those with scintigraphic evidence of partial thyroid autonomy were excluded. FNAC was evaluated by three qualified pathologists, and the remainder of the preparation was used for RNA extraction that was further reverse-transcribed by polymerase chain reaction (RT-PCR). As a test of confidence, the PCR product of four nodules was sequenced and proved to be the PCR-amplified product corresponding to the RET/PTC modification of the cDNA. Ultrasound examination was repeated at 6 months and then at yearly intervals.

**RESULTS**
In 19 (15%) of 125 patients a rearrangement could be identified. The mean follow-up period was 31 months for RET/PTC-positive and 37 months for RET/PTC-negative nodules. In the group of RET/PTC-positive nodules, three cases had to be excluded because of rapid growth justifying early thyroidectomy. The number of nodules that were finally surgically removed was not indicated. During the observation period, the volume of RET/PTC-negative nodules increased from 2.61 to 3.18 ml and in the RET/PTC-positive cases from 3.04 to 5.04 ml. In both groups, the increase was highly significant. The increase in the RET/PTC-positive nodules was clearly and significantly higher than in the RET/PTC-negative ones. Expressed as a percentage growth rate per month, the RET/PTC-positive nodules again increased significantly faster than the negative ones.

**CONCLUSIONS**
The results of RT-PCR assay performed on material obtained from thyroid nodules by FNAC—a highly demanding technique (1)—lend support to the assumption that a RET/PTC rearrangement might be one of the important molecular mechanisms contributing to enhanced cell replication in rapidly growing benign nodules. The results also demonstrate that by itself the rearrangement is not carcinogenic, since thyroid nodules harboring this mutation do not acquire an aggressive nature. The authors do not suggest that their technique should play a role in the diagnostic workup of thyroid nodules. This cautious conclusion is based on the evidence that many RET/PCR-negative nodules were also found to have a rather high growth rate, thus indicating that other growth factors must be involved in promoting the growth of benign as well as malignant thyroid nodules.

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In this cohort, many RET/PTC-positive but also some RET/PC-negative nodules showed considerable growth over a relatively short period of observation. This is rather unexpected, since most thyroid nodules are reported to grow rather slowly or even to remain at least temporarily stable. Possibly, moderate iodine deficiency that is still prevalent in Italy, could represent a additional goitrogenic stimulus. Nevertheless, the mean growth rate of all nodules harboring the RET/PTC rearrangement was unequivocally higher than in the negative nodules. The results certainly stress the importance of the RET/PTC rearrangement for growth rate, but they also clearly suggest the presence of other unknown growth-promoting mechanisms. The heterogeneity of the results is in no way surprising, given the notorious intercellular functional heterogeneity among thyrocytes. The authors consider as possible explanations individually differing intensity of RET/PTC expression.

The authors cautiously consider the possibility that the RET/PTC rearrangement detected on FNAC could help clinicians to choose surgery as the first-line therapeutic approach in a given thyroid nodule. However, most clinicians would probably advise surgical treatment to any patient with a steadily growing thyroid nodule irrespective of whether or not RET/PTC rearrangement was present.

In summary, this careful work adds a valuable brick to the ultimate construction of a multistory building that represents the intricate network of growth-promoting mechanisms in benign tumors.

— Albert G. Burger, MD

REFERENCES
THE INCIDENCE OF BRAF MUTATION IN PAPILLARY THYROID CANCERS IS INCREASING


SUMMARY

BACKGROUND
The incidence of papillary thyroid cancer (PTC) has increased greatly in the past decade. To investigate the reasons for this, the authors studied the molecular changes in the PTCs they have seen during the past 15 years.

METHODS
The authors studied 628 consecutive patients with PTC seen from 1991 through 2005. They had performed molecular testing on 228 tumor samples by analysis for the BRAF V600E point mutation, RET/PTC1, RET/PTC3, and NTRK1 rearrangements, and hotspot point mutations in KRAS and NRAS. They performed a time-trend analysis for the mutations over the three consecutive 5-year periods.

RESULTS
The authors found no differences between the three groups in the age at diagnosis, sex, ethnicity, primary tumor size, tumor–node–metastasis cancer stage, or rate of extrathyroidal invasion in the 628 patients. However, among the 228 tumor samples, the tumors in the most recent group, years 2001 to 2005, were smaller than those of the earlier groups. Somatic mutations were found in 92% of this group, but only 68% of tumors from 1991 to 1995 and 64% of tumors from 1996 to 2000 (P<0.002). The BRAF mutation was found in 88% of 2001–2005 tumors, 51% of 1991–1995 tumors, and 43% of 1996–2000 tumors. The higher rate of BRAF mutation in the most recent group did not correlate with any clinical variables. The incidence of the other mutations studied was not significantly different among the groups, although there were fewer RET/PTC3 mutations in the 2001–2005 group (4%) than in the other groups (16 and 15%, respectively).

CONCLUSION
The rate of the BRAF V600E mutation in papillary thyroid cancer increased significantly over a 15-year period at the authors’ institution. This finding suggests that the higher rate of BRAF mutation may explain the increasing incidence of papillary thyroid cancer.

COMMENTARY
The very high rate of BRAF mutation in PTC in a San Franciscan population that was about 17% Asian is the first report I have seen that shows a rate of the BRAF mutation in the United States that is similar to that reported in Korea, where 90% of PTCs have the BRAF mutation (1). The BRAF mutation has not been associated with radiation exposure, but the RET/PTC3 mutation was associated with radiation exposure from Chernobyl (2). The data suggest that an environmental toxin may be playing a role in the epidemic of PTC that we now find. Fortunately, our sensitive methods for finding tumors at an early stage may prevent these tumors from spreading and recurring. Although retrospective analyses of PTC with BRAF mutations showed that they were more aggressive than PTC without this mutation (3), this was not apparent in the study under discussion. However, no data on recurrence were presented. Nevertheless, I speculate that finding the BRAF mutation in PTC tumors <2 cm is not likely to have an ominous prognosis because these tumors are generally associated with excellent survival after appropriate surgery.

— Jerome M. Hershman, MD

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THE INCIDENCE OF BRAF MUTATION IN PAPILLARY THYROID CANCERS IS INCREASING

References


CHEMOKINES CXCL9 AND CXCL11 ARE INVOLVED IN THE INITIAL AUTOIMMUNE RESPONSE OF AUTOIMMUNE THYROIDITIS


SUMMARY

BACKGROUND
Chemokines induce chemotaxis of different leukocyte subtypes. In many inflammatory diseases, they recruit these leukocytes to settle at the site of injury. CXCL10 is known to be inducible by interferon γ, as are CXCL9 and CXCL11. In a considerable percentage of patients, interferon γ therapy produces autoimmune thyroiditis, suggesting that these cytokines are playing a crucial role in the initial events of thyroid autoimmune disease and possibly also in the development of transient hyperthyroidism or hypothyroidism. They interact with one single receptor, CXCR3, that is expressed in some subgroups of T helper and T killer cells (1).

The role of one chemokine, CXCL10, has been documented in thyroid cell cultures, and serum levels of CXCL10 have been shown to be increased in autoimmune thyroiditis. Moreover, in cultured thyroid cells, interferon γ and tumor necrosis factor a are able to induce other chemokines, such as CXCL9 and CXCL11. The aim of this study was to measure the blood levels of CXCL9 and CXCL11 in patients with autoimmune thyroiditis.

METHODS AND RESULTS
This study was performed in a single center, at which 141 consecutive patients with autoimmune thyroiditis were investigated; 81% of these patients had antithyroid peroxidase antibodies, 74% had antithyroglobulin antibodies, and 26% were subclinically hypothyroid. At ultrasound examination, hypoechogenicity was found in 82% and hypervascularization in only 39%. Two control groups consisted of patients with a normal thyroid or with multinodular goiter; all of these subjects had also undergone a complete thyroid workup. Any patient receiving drugs that might interfere with thyroid function was excluded.

The results for CXCL9 and CXCL11 are qualitatively very similar. The serum levels of both chemokines were increased in autoimmune thyroiditis above those found in the controls. They were higher in the presence of hypothyroidism and/or of a hypoechogenic gland. In addition, elderly patients had, in general, higher values than young patients. The difference was particularly marked in patients above 50 years of age as compared with patients below 50. It is interesting that even in the control groups there was a significant correlation between serum levels of chemokines and age.

CONCLUSIONS
CXCL9 and CXCL11 can now be added to the list of chemokines intimately involved in the initial immune response of autoimmune thyroiditis. When stimulated by interferon γ or other appropriate cytokines, thyrocytes from normal or pathologic specimens will respond with the production of chemokines. Obviously, some other cell types will respond similarly. The mechanism is therefore ubiquitous and not confined to the thyroid.

The authors do not propose a diagnostic value for the serum determinations of CXCL9 and CXCL11.

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COMMENTARY

Another little piece is added to the mosaic pattern of the pathogenesis of autoimmune thyroiditis. It still does not answer the question of why the thyroid is so often affected by autoimmune processes. Also, one may argue that the process is not specific for the thyroid. It is possible that this frequently occurring and benign thyroid disease may help to elucidate the origin of autoimmunity in general.

—Albert G. Burger, MD

REFERENCE

EUTHYROID PATIENTS WITH CHRONIC HEPATITIS C TREATED WITH PEGYLATED INTERFERON ALFA AND RIBAVIRIN SHOW SIMILAR CHANGES IN CELLS THAT COORDINATE IMMUNE RESPONSES AND MAINTAIN IMMUNOLOGIC TOLERANCE, BUT DISPLAY A SPECTRUM OF DIFFERENT THYROID DISEASES


SUMMARY

BACKGROUND
Interferon-alfa treatment can precipitate a wide spectrum of thyroid diseases in susceptible individuals, probably through actions on the immune system as well as through toxic effects on the thyroid, but the precise mechanisms and/or genetic propensities involved remain unknown.

METHODS
A total of 120 Spanish patients with chronic hepatitis C who had never undergone treatment were given weekly peginterferon alfa-2a plus ribavirin 1 to 1.2 g daily for 48 weeks (for patients with hepatitis C virus [HCV] genotype 1 or 4) or plus ribavirin 0.8 g daily for 24 weeks (for HCV genotype 2 or 3). They were then followed for 24 weeks to determine whether their HCV RNA levels remained suppressed. All patients had normal thyroid-function tests and negative antithyroid tests at baseline. Any patient who was positive for hepatitis B surface antigen, had alcoholism, was an intravenous-drug abuser, or had the human immunodeficiency or other virus was excluded from the study. Peripheral-blood mononuclear cells (PBMCs) were prepared and frozen at the beginning of the study, at the midpoint of treatment, at the end of treatment, and 24 weeks after the end of treatment.

Some form of thyroid disease developed in 11 patients: 5 had destructive thyroiditis, 3 had Hashimoto’s thyroiditis, 1 was euthyroid but had positive antithyroid antibodies, 1 had Graves’ disease, and 1 had non-autoimmune hypothyroidism. Additional PBMCs were drawn when thyroid disease was detected. Eleven patients who had undergone the same treatments were retrospectively selected to be controls, based on the sex and age of the patients in whom thyroid disease had developed. The controls apparently were not matched based on body-mass index or smoking status.

RESULTS
Flow cytometry was performed on PBMCs obtained from patients when their thyroid diseases appeared, and the lymphocyte populations were compared with the PBMCs obtained from the matched controls at the midpoint of their treatment. The PBMC’s obtained from the patients upon the development of thyroid disease displayed a higher response in type 1 helper T (Th1) cells, which coordinate immune responses, and a greater percentage of natural T regulatory cells, which maintain immunologic tolerance. No differences in lymphocyte populations were detected among the different thyroid diseases that developed. Development of thyroid disease was not associated with the patients’ antiviral responses.

CONCLUSIONS
Peginterferon alfa-2a plus daily ribavirin affected Th1 cell responses and the percentage of T regulatory cells in patients in whom a variety of thyroid diseases developed. continued on next page
Prior to therapy, some patients with hepatitis C already have positive antithyroid antibody levels, although the percentage varies according to the assays used, the geographic location, and the genetic makeup of the population under study. Products from a variety of viruses, including hepatitis C, have been detected in thyroid tissue from patients with Hashimoto’s thyroiditis, so it is possible that antiviral responses could be involved in the induction of thyroid diseases in some of these individuals. However, the patients in the study under discussion did not have antithyroid antibodies or altered thyroid function before they started treatment, so it would seem reasonable to attribute the thyroid diseases that appeared to the therapy they received. Boceprevir, a new anti-HCV drug, was recently studied in a larger group of patients with chronic HCV infection who had a TSH of 0.8 to 1.2 times normal or who were clinically euthyroid with a normal serum T₃ and T₄ levels at the start of the study (1). In the group of 363 patients who were given the standard peginterferon/ribavirin regimen, only 1 had hypothyroidism, while none of the 368 patients given boceprevir along with peginterferon/ribavirin for 24 weeks became hypothyroid. Assuming the assays used and the follow-up periods were reasonably similar to those in the study under discussion, the patients in the two studies seemed to differ greatly in their susceptibility to peginterferon/ribavirin-induced thyroid disease. Nonetheless, boceprevir may hold promise for an anti-HCV regimen that will cause less thyroid disease in euthyroid patients with hepatitis C.

— Stephen W. Spaulding, MD

REFERENCE

PENDRED SYNDROME CAN BE COMPLICATED BY SEVERE ALKALOSIS


SUMMARY

BACKGROUND

Pendred syndrome, the most common form of syndromic deafness, is well known to thyroidologists because some patients with this syndrome present with a diffuse or multinodular goiter with or without moderate hypothyroidism. The main characteristic of Pendred syndrome is congenital or acquired sensorineural deafness. The molecular basis of the disease is a biallelic defect of pendrin, a multifunctional anion exchanger encoded by the SLC26A4/PDS gene (1,2). This protein is localized at the apical border of the follicular cell and appears to be involved in iodide transport into the lumen. In the inner ear, pendrin transports bicarbonate into the endolymph and absorbs chloride. It has also been identified in the kidney, where it secretes bicarbonate and reabsorbs chloride. Under physiologic conditions, however, there is no detectable renal phenotype. So far, alkalosis has been reported to have developed in only one pediatric patient with Pendred syndrome. The case under discussion represents the second observation.

CASE REPORT

This 46-year-old female patient had childhood-onset sensorineural hearing loss. Mild hypothyroidism was diagnosed in adulthood and treated for 1 year before the current event. The patient, a severe alcoholic, was discovered on the floor in a confused state with rigid limbs. In the hospital, severe potassium, chloride, and magnesium deficiencies (K, 1.4 mmol/L; Cl, 86 mmol/L; Mg, 0.19 mmol/L) and bicarbonate and base excess (bicarbonate, 45 mmol/L; base excess, +20.4) were recorded. She was treated with fluid and electrolyte replacement. Recovery was complicated by a respiratory arrest and an episode of atrial fibrillation. A review of her medical history revealed that she had had a similar episode of hypokalemia 1 year earlier. The diagnosis of Pendred syndrome was established by magnetic resonance imaging of the inner ear, which showed a characteristic enlargement of the endolymphatic system, and by mutational analysis of the SLC26A4 gene.

CONCLUSIONS

Under normal conditions, problems with electrolyte and acid–base imbalance are not seen in patients with Pendred syndrome because with a Western acid-rich diet, the kidneys rarely need pendrin for bicarbonate excretion and chloride reabsorption. Yet experimental studies indicate a much larger role for renal pendrin, also affecting blood pressure and extracellular volume. Inhibition of the function of pendrin may become limiting in selected instances and result in metabolic alkalosis. As illustrated by this patient, the limited capacity for bicarbonate excretion may become deleterious in cases of vomiting and alcohol abuse; other causes include eating an exclusively vegetarian diet or having diarrhea.

COMMENTARY

Being aware of acute alkalosis as a rare but life-threatening complication in patients with Pendred syndrome is important, since many of us take care of patients with this syndrome. In addition, the role of pendrin in the renal bicarbonate–chloride balance may be far more important than expected based on this case report. Pendrin is likely to play a crucial role in the control of blood pressure; the antihypertensive action of thiazides may in part be due to targeting renal pendrin (3).

— Albert G. Burger, MD

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PENDRED SYNDROME CAN BE COMPLICATED BY SEVERE ALKALOSIS

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