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Microcalcification and Intranodular Coarse Calcification Are Often Found on Preoperative Ultrasounds of Papillary Thyroid Carcinoma

Stephanie L. Lee

Kim BK, Choi YS, Kwon HJ, Lee JS, Heo JJ, Han YJ, Park YH, Kim JH. Relationship between patterns of calcification in thyroid nodules and histopathologic findings. Endocrine J. October 6, 2012 [Epub ahead of print]. doi: 10.1507/endocrj.EJ12-0294.

SUMMARY

Background

Thyroid nodules are commonly seen in adults. Studies suggest a prevalence of 2% to 6% on palpation, 19% to 35% on ultrasound, and 8% to 65% in autopsy data (1). Most professional endocrine professional societies' guidelines, including the 2009 ATA guidelines (2), recommend sonographic examination as part of the evaluation for malignancy of all thyroid nodules. The sonographic features of microcalcification are highly specific (89.1% to 96.8%) but not sensitive (20% to 24.3%) for papillary thyroid carcinoma (3,4). Macrocalcification has previously been associated with an increased risk of thyroid malignancy (5). The objective of this study was to determine which pattern of calcification is predictive of malignancy in a large number of thyroid nodules confirmed as benign or malignant after resection.

Methods and Results

The aim of this study was to determine which pattern of calcification is associated with thyroid malignancy. This is a single-institution retrospective study of 1431 thyroid nodules in 1078 patients between January 2008 and July 2011 who had a preoperative ultrasound prior to thyroid surgery. The male:female ratio was 5.3:1 and the mean (±SD) age was 47.2±11.1 years. The reason for surgery was usually increased risk of malignancy or cosmetic concerns. Thyroid ultrasound was performed by two radiologists with a 5- to 12-MHz linear array

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transducer. All images were independently reviewed by an endocrinologist whose specialty was thyroid disease. The calcifications were categorized as microcalcification (fine stippling, <2 mm), annular-like peripheral calcification (coarse calcification around the surface of the nodule in an eggshell pattern), crescent-like calcification (irregular curved line of coarse calcification), intranodular coarse, disorganized calcification >2 mm with acoustic shadowing within a nodule, or a calcified spot (single spot of macrocalcification not associated with a discrete nodule). The average size of the resected nodule was 1.2±0.8 cm (range, 0.1 to 6 cm). A total of 91.1% of the resected nodules were thyroid cancer and 8.9% were benign nodules; 94.7% of the malignancies were papillary thyroid carcinoma. The data were analyzed as a frequency with a 2-by-2 table to calculate sensitivity, specificity, and positive predictive value. Calcifications were detected in 38.6% of all nodules, 40.2% of malignant nodules, and 22.2% of benign nodules. The distribution of calcification in malignant nodules was microcalcification in 42.9%, intranodular in 26.5%, calcified spot in 13.4%, crescent in 11.1%, and annular-type in 5.9%. The only forms of calcification associated with thyroid malignancy were microcalcification (odds ratio [OR], 3.5; 95% CI, 1.6 to 7.7; P<0.001) and intranodular coarse calcification (OR, 2.4; 95% CI, 1.1 to 5.6; P = 0.035).

Conclusions

In this retrospective study, thyroid malignancy frequently was found on preoperative ultrasound to contain microcalcification (42.9%) and intranodular coarse calcification.

ANALYSIS AND COMMENTARY

Sonographic evidence of calcification is found in both benign and malignant nodules. This retrospective study is significant because of the large number of patients who had both a preoperative thyroid ultrasound and thyroidectomy to confirm pathology. A limitation of this study is that more than 90% of the subjects had thyroid cancer. The benign nodule cohort contained only 126 nodules, as compared with the cancer cohort, which contained 1305 nodules. Thus, the frequency of the calcification patterns cannot provide accurate statistics of sensitivity or specificity for detecting thyroid malignancy based on a preoperative ultrasound. This study does confirm that both microcalcification and intranodular coarse calcification are commonly seen in thyroid malignancy. It is important to recognize that other forms of calcification (annular, crescent, spot) can be seen in thyroid cancer and are not a sonographic sign that a thyroid nodule is benign.

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Weak Evidence Suggests That Multinodular Goiter Is Less Likely to Harbor a Malignancy than a Solitary Nodule

Jerome M. Hershman

Brito JP, Yarur AJ, Prokop LJ, McIver B, Murad MH, Montori V. Prevalence of thyroid cancer in multinodular goiter vs. single nodule: a systematic review and meta-analysis. Thyroid. October 15, 2012 [Epub ahead of print].

SUMMARY

Background

Many years ago the dogma was that multinodular goiter was usually a benign condition and, in contrast, a single "dominant" nodule was much more likely to be malignant than the nodules in a multinodular goiter. However, various studies have contradicted this belief and convinced endocrinologists to evaluate nodules in multinodular goiter for the possibility of malignancy. This study is a systematic review of the prevalence of malignancy in the nodules of multinodular goiter versus that in single nodules.

Methods

The authors reviewed MEDLINE and other databases to find studies of adults with diagnoses of multinodular goiter or single thyroid nodules by ultrasound who underwent FNA of a nodule or surgery. FNA results indicating malignancy required pathological diagnosis on the resected specimen. "Hot" nodules were excluded from the study.

Results

After screening 648 articles, only 14 published between 1987 and 2010 were considered suitable for inclusion in the review. These studies included 20,723 patients in the single-nodule group and 23,565 in the multinodular group. In a meta-analysis of these studies, the risk of thyroid cancer was significantly lower in the multinodular group than in the single-nodule group (odds ratio [OR], 0.8; 95% CI, 0.67 to 0.96) with some inconsistency among the studies. The four studies in the United States did not support this conclusion; the odds of thyroid cancer in multiple versus single nodules did not differ (OR, 1.00, 95% CI, 0.79 to 1.26). Based on whether a region was considered iodine-deficient, there was an association between iodine deficiency and the finding of lower risk in multinodular goiter.

Conclusions

Thyroid cancer may be less frequent in multinodular goiter as compared with single nodules, particularly outside the United States.

ANALYSIS AND COMMENTARY

I used to believe that multinodular goiter was nearly always a benign condition, but my belief was shattered by the 1992 report of Belfiore et al. from Italy, who reported that the frequency of thyroid cancer in patients with a solitary nodule was not different from the frequency in patients with multiple nodules—about 5% (1). This conclusion about frequency (prevalence) was confirmed by the study of Frates et al. in Boston, who reported the same prevalence of cancer in multinodular goiter and in single nodules (about 15%), although the single nodule was twice as likely to be malignant as a nodule in a multinodular goiter; biopsy of each nodule >1 cm in a multinodular goiter increased the prevalence so that it became the same in multinodular goiter as that in the single nodule (2).

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The results of this review are highly influenced by one study, by Rago et al. in Pisa. They reported that papillary thyroid cancer (901 cases) was more frequent in solitary nodules (446 of 13,549 [3.3%]) than in multinodular goiter (411 of 19,923 [2%], P<0.0001) (3). None of the other studies showed a significant difference in odds ratios, but the meta-analysis that included this study supported the conclusion noted above.

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Fine-Needle Aspiration Biopsy with BRAF Analysis and Elastography are Slightly More Efficient in Diagnosing Papillary Thyroid Cancers than FNAB and Thyroid Ultrasound

Albert G. Burger

Nacamulli D, Nico L, Barollo S, Zambonin L, Pennelli G, Girelli ME, Casal Ide E, Pelizzo MR, Vianello F, Negro I, Watutantrige-Fernando S, Mantero F, Rugge M, Mian C. Comparison of the diagnostic accuracy of combined elastosonography and BRAF analysis vs cytology and ultrasonography for thyroid nodule suspected of malignancy. Clin Endocrinol (Oxf) 2012;77:608-14.

SUMMARY

Background

Diagnostic workup of thyroid nodules remains unsatisfactory, since 15% to 30% of samples obtained by fine-needle aspiration biopsy (FNAB) are classified as indeterminate. In these cases, thyroidectomy or lobectomy is indicated, even though a thyroid carcinoma is ultimately confirmed in less than 20% of these cases. In recent years many attempts at improving the diagnostic yield have been published. For instance, studies using the microarray technique to analyze a large number of genes show promise (1,2). Unfortunately, the test samples have to be shipped to specialized laboratories, and the investigation is still very expensive. In the present article, the authors analyze the performance of another approach that is available in regional centers. The authors combine elastography (ultrasound elastography [USE]), an improved ultrasound method measuring tissue stiffness, with measurement of the already well-established tumor marker BRAF in the FNAB. A total of 45% to 60% of papillary cancers harbor a point mutation of this gene, primarily the BRAF V600E mutation but other BRAF mutations (K601E and AKAP9-BRAF) mutations are also known to occur (3). However, BRAF mutations are rare in follicular thyroid cancers, and these tumors do not show increased tissue stiffness.

Methods

This retrospective study extended from 2009 to 2011. A total of 164 nodules were studied. Freehand USE was done using a real-time scale of 1 to 5, where 5 corresponds to the highest tissue stiffness. BRAF mutations were identified through direct sequencing and by mutant allele–specific PCR amplification.

Results

The results of the histologic workup were as follows: 74 (45%) were benign nodules and 90 were malignant; 73 of the malignant nodules were classical papillary thyroid cancers, 10 were the follicular variant of papillary thyroid carcinoma (PTC), 5 were follicular cancers, and 2 were medullary cancers. Of these nodules, 37 had a diameter <1 cm and 58 were positive for BRAF mutations, 54 of which harbored the mutation V600E. BRAF mutation analysis was particularly useful in nodules with high elasticity (scale 1), in which the malignancy would have been missed without it. BRAF mutations were detected in 70% of all PTCs.

By combining BRAF analysis with USE, 105 nodules were classified as suspicious; 86 (82%) proved to be malignant. Using classical ultrasound and FNAB, 63% of the suspicious nodules that were operated on proved to be malignant. The predictive value of the combined tests turned out to be clearly superior for USE and BRAF as compared with ultrasound and FNAB. In particular, the specificity was markedly better (predictive value 74% as compared with 28%). Ultrasound and FNAB still left 50 cases in the "intermediate" group. Only 9 (18%) proved to be thyroid

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cancers at operation. When using USE and BRAF mutations, 15 of 31 (48%) turned out to be cancers.

Conclusions

This retrospective study concerns thyroidectomies and/or lobectomies carried out for 164 thyroid nodules, of which a very high percentage were revealed to be cancers. They were investigated by ultrasound, USE, FNAB and BRAF mutations. The combined use of BRAF and USE was useful since in some elastic (scale 1) nodules BRAF mutations were positive; also some stiff (scale 4), but BRAF-negative, nodules were revealed to be malignant. Only the combination of the two results suggested the need for operation. Nevertheless, in a few cases BRAF analysis and USE failed to recognize the malignant nature of the nodule.

ANALYSIS AND COMMENTARY

The authors themselves suggest that this preliminary study should be followed by a prospective multicenter study. Other approaches, such as the gene microarray technique should be included. Yet, the cost of such an experiment would be very high and the success probably doubtful.

The present study, though interesting, has some clear shortcomings. For instance, only patients who underwent surgery are included in the study. This creates a considerable bias, since it is unlikely that in this center all patients underwent surgery. Moreover, although follicular cancers are mentioned, no separate results were given, despite the fact that they are known to be different in terms of BRAF mutation frequency and elasticity. Furthermore, it is not clear why the authors did not compare the combination of ultrasound and BRAF mutations instead of ultrasound and FNAB. Finally, even though not discussed specifically in the text, but shown in one figure, approximately 5% to 7% of nodules considered as benign based on USE scale 1 and absence of BRAF mutations were eventually identified as being malignant. Therefore, even in this situation, the clinical decision cannot rely fully on these two criteria.

However, the approach has the advantage of being easily feasible with a moderate increase in cost. Also, the technique of USE is still in a developing stage; at present, the more powerful, less subjective, and more objective shear wave elastography is becoming available (4). It is therefore likely that in the near future the information about the elasticity of thyroid nodules will become a routine addition to the present ultrasound techniques, although it brings only a small advantage over the currently available techniques.

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Smoking May Decrease the Incidence of Thyroid Cancer in Postmenopausal Women

Jerome M. Hershman

Kabat GC, Kim MY, Wactawski-Wende J, Rohan TE. Smoking and alcohol consumption in relation to risk of thyroid cancer in postmenopausal women. Cancer Epidemiol 2012;36:335-40. Epub April 22, 2012; doi: 10.1016/j.canep.2012.03.013. .

SUMMARY

Background

Thyroid cancer is the eighth most common cancer in women, and its incidence is increasing. No risk factors other than ionizing radiation have been identified for differentiated thyroid cancer. Studies of the relationship of thyroid cancer with cigarette smoking have been contradictory. Most studies of alcohol consumption have found no association with thyroid cancer. The current study is an analysis of the association of smoking and alcohol consumption in the Women's Health Initiative (WHI), a large multicenter study designed to advance the understanding of causes of major chronic diseases in postmenopausal women.

Methods

The study assessed the association of smoking and alcohol intake with risk of thyroid cancer in a cohort of 159,340 women enrolled in the WHI. A self-administered questionnaire recorded smoking habits with regard to ever smoking, age at starting, whether a current smoker, age at quitting, and number of cigarettes smoked per day. The number of alcoholic drinks per month, week, and day were also recorded. Cox proportional-hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals for the associations of smoking and alcohol intake with risk of thyroid cancer. Tests were also performed for the interaction of alcohol intake and smoking and thyroid cancer risk.

Results

There were 331 cases of thyroid cancer, of which 276 were papillary thyroid cancers (PTCs). At baseline, patients with thyroid cancer were significantly younger (61.9 vs. 63.2 years) and taller (163.3 vs. 161.8 cm), had lower alcohol intake, and had a much greater frequency of thyroid nodules and goiter than patients who did not have cancer. Women who had smoked for <20 years were at elevated risk for thyroid cancer (HR, 1.35; 95% CI, 1.05 to 1.74). Smokers of >40 pack-years had a significantly reduced risk of PTC based on 8 exposed cancer cases (vs. 12,300 smokers who did not have cancer) (HR, 0.44; 95% CI, 0.21 to 0.89). Current smokers (11,200) had a reduced risk for PTC (HR, 0.34; 95% CI, 0.15 to 0.78), but there were only 6 patients with PTC for comparison.

Alcohol consumption was not associated with an altered risk of thyroid cancer, nor was the amount of alcohol associated with the risk of thyroid cancer. There was no interaction between smoking and drinking on the risk of thyroid cancer.

Conclusions

"Our findings suggest that current smoking and having higher pack-years of exposure are associated with a modestly reduced risk of thyroid cancer, whereas alcohol consumption does not appear to affect risk."

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ANALYSIS AND COMMENTARY

For people who are prejudiced against smoking, as I am, these results are disquieting. In November 2012 the Chancellor of UCLA announced that UCLA will become a tobacco-free campus starting April 2013, and I welcomed this plan. The authors reference five studies that showed an inverse association of thyroid cancer and smoking, mainly case–control studies, so their finding is not novel. How can the findings be explained? Smoking is associated with reduced serum TSH levels based on an analysis of the third National Health and Nutrition Examination (NHANES III) data (1). Smokers had a reduced frequency of elevated serum TSH, and within the normal range of serum TSH, smokers had a twofold increase in the incidence of low-normal TSH (0.1 to 0.4 mU/L) as compared with nonsmokers. Abundant data exist showing that higher serum TSH is associated with increased frequency of malignancy in patients with thyroid nodules (2). Could TSH suppression by smoking prevent the development of cancer in thyroid cells that harbor oncogenic mutations?

Another possibility is that the broad array of cancers and vascular diseases induced by smoking causes deaths and, in a sense, prevents the development of other diseases, such as thyroid cancer.

Because of the very large number of subjects in the WHI, trivial differences become significant, such as the taller height and younger age of the patients with thyroid cancer. One major limitation is that the data from this study apply only to postmenopausal women.

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Weight Gained after Smoking Cessation May Be Caused by Onset of Hypothyroidism

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Carlé A, Bülow Pedersen I, Knudsen N, Perrild H, Ovesen L, Banke Rasmussen L, Jørgensen T, Laurberg P. Smoking cessation is followed by a sharp but transient rise in the incidence of overt autoimmune hypothyroidism—a population-based, case–control study. Clin Endocrinol 2012;77:764-72.

SUMMARY

Background

Current smoking is associated with a low prevalence of thyroid autoantibodies; however, the thyroid autoantibody level increases following smoking withdrawal and could be a risk factor for the development of hypothyroidism. The aim of the authors was to assess the association between smoking habits (smoking cessation in particular) and the development of autoimmune hypothyroidism.

Methods

This was a population-based, case–control study conducted from 1997 through 2000. The Danish Investigation of Iodine Intake and Thyroid Diseases (DanThyr) prospectively identified all patients with newly diagnosed overt hypothyroidism in a Danish population. A total of 140 (59.5% of all patients diagnosed with autoimmune hypothyroidism) agreed to participate. Patients were identified prospectively by population monitoring (2,027,208 person-years of observation) of all thyroid-function tests performed in the two well-defined geographical areas: Aalborg, which had moderate iodine deficiency, and Copenhagen, which had only mild iodine deficiency. All subjects with a high serum TSH (>5.0 mU/L) in combination with a low T_4 estimate identified by the register were individually scrutinized to verify or disprove new overt hypothyroidism; subjects with antibody concentrations above the functional sensitivity given by the manufacturer (TPOAb, >30 kU/L, TgAb, >20 kU/L) were regarded as antibody-positive. Only patients with primary autoimmune hypothyroidism were considered for this study. Individually, age-, sex-, and region-matched euthyroid controls (n = 560) were simultaneously included from the same population. Participants gave details on smoking habits, including smoking withdrawal, and other lifestyle factors. Smoking habits were verified by measuring urinary cotinine, a nicotine metabolite.

Results

Incident hypothyroidism was very common in people who had recently stopped smoking (odds ratio [OR] vs. never smokers (95% CI): <1 year after quitting smoking, 7.36 [2.27 to 23.9]; 1 to 2 years, 6.34 [2.59 to 15.3]; 3 to 10 years, 0.75 [0.30–1.87]; >10 years, 0.76 [0.38 to 1.51]). Results were consistent in both sexes and irrespective of age. Within 2 years after smoking cessation, the percentage of cases of hypothyroidism attributable to smoking cessation was 85%. Current smoking was not associated with an altered risk of overt hypothyroidism (OR, 0.92 [0.57 to 1.48]). The authors found no difference in years of smoking, pack-years of smoking, or preferred type of tobacco consumption.

Conclusions

The risk of receiving a diagnosis of overt autoimmune hypothyroidism is increased more than six-fold in the first 2 years after smoking cessation. Clearly, smoking cessation is vital to prevent death and severe disease. However, awareness of hypothyroidism should be high in people who have recently quit smoking, and virtually any report of symptoms should prompt thyroid-function testing.

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ANALYSIS AND COMMENTARY

The possible association of tobacco smoking and thyroid disease has been reported in the literature for some time, such as the higher incidence of goiter in smokers (1), risk of Graves' disease (2), development of autoimmune thyroiditis (3), and worsening of Graves' orbitopathy (4). However, several studies have had conflicting results with regard to smoking's relationship to hypothyroidism (5). The appearance of thyroid antibodies after smoking cessation has been reported (6). In the present study, the cases and controls showed no statistical differences between years of smoking, pack-years of smoking, and type of smoking. There was also no statistical difference between the two geographical areas, one with mild iodine deficiency and the other with moderate iodine deficiency. The high incidence of autoimmune hypothyroidism within the first 2 years after smoking cessation is striking; the median serum TSH was 54.5 mU/L, and as compared with controls, patients newly diagnosed with hypothyroidism had a 7.5 kg higher body weight, which the authors attributed to fluid accumulation. Weight gain and tiredness are not unusual symptoms following tobacco cessation, and these are often attributable to "lack of nicotine." Advising our patients to quit cigarette smoking is a routine recommendation in our daily medical practice. Perhaps we clinicians should pay more attention to our patients' medical history and keep in mind the possibility of hypothyroidism as the cause of symptoms that appear after smoking cessation.

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The Allan–Herndon–Dudley Syndrome: How Common Is It, and Does Normalizing Thyroid Function Tests in Such Patients Improve Any Clinical Parameters?

Stephen W. Spaulding

Visser WE, Vrijmoeth P, Visser FE, Arts WF, van Toor H, Visser TJ. Identification, functional analysis, prevalence and treatment of monocarboxylate transporter 8 (MCT8) mutations in a cohort of adult patients with mental retardation. Clin Endocrinol. August 28, 2012 [Epub ahead of print]. doi: 10.1111/cen.12023.

SUMMARY

Background

Thyroid hormone transporters are expressed on the plasma membranes of cells, where they can influence both the uptake and the efflux of thyroid hormones. The monocarboxylate transporter 8 (MCT8) is an important and widely expressed transporter of several thyronines. Patients with the Allan–Herndon–Dudley syndrome present in infancy with hypotonia, weakness, and failure to gain weight. They have global developmental delays in childhood, and they display spasticity and hyperreflexia as adults. Their thyroid-function tests show a characteristic pattern—high T_3, low-normal T_4, and high-normal TSH—that reflect mutations in MCT8 affecting its activities. The hypothalamic–pituitary axis seems to have reduced sensitivity to T_3, whereas the high circulating level of T_3 produces hyperthyroid responses in the kidney, liver, and cardiovascular system of these patients. (Interestingly, MCT8 is also expressed in the thyroid gland, where it is involved in the secretion of thyroid hormones). MCT8 is found on the X chromosome; female carriers generally are asymptomatic, but may display mild abnormalities on thyroid-function tests (1). The current study used less stringent thyroid hormone criteria to screen men institutionalized for mental retardation to look for additional patients with MCT8 mutations.

Methods

A study on the thyroid origin of psychomotor retardation recruited about 500 institutionalized men from centers throughout the Netherlands (2). The serum levels of T_4, FT_4, TSH, T_3, rT_3, and sex hormone binding globulin (SHBG) were determined. For patients whose T_3 was above the 80th percentile and whose T_4 was below the 20th percentile, the coding region of the MCT8 gene was sequenced. Mutant MCT8 genes were transfected into JEG3 cells, which do not express MCT8, and the percent of T_4, T_3, and rT_3 taken up was compared to the uptake of cells expressing the wild-type MCT8 gene. In one patient, the efficacy of combining antithyroid drug with L-T_4 was assessed.

Results

Eight patients were found to meet the less stringent limits on thyroid-function tests, and sequencing of their MCT8 genes uncovered two new mutations (L492P and a synonymous mutation, T162T). The synonymous T162T sequence did not affect the uptake of T_4, T_3, or rT_3 in JEG cells—as might have been anticipated—so this mutation was a coincidental finding, unrelated to the patient's neurologic condition. The L492P mutant, when expressed in JEG cells, had somewhat more active transport activity than most previously studied MCT8 mutations. A third patient was also uncovered: his mutation was a 3-base-pair deletion (F501del) that had previously been studied in that patient's nephew, who had a slightly milder phenotype, and whose fibroblasts showed more impairment of T_4 and T_3 efflux than their impairment in T_4 and T_3 uptake. Defective uptake was confirmed when the current patient's mutant MCT8 gene was expressed in JEG cells. This patient was initially treated

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with PTU alone, which caused the serum T_3 level to fall to low-normal levels by 15 weeks, but the FT_4 fell below normal and the TSH rose, so L-T_4 was added to the PTU treatment. After about 20 weeks of treatment with L-T_4 plus PTU, the TSH, T_4, and T_3 levels normalized. A slight improvement in the patient's eating and aggressive behavior was also noted. The serum level of both bone-specific alkaline phosphatase and SHBG normalized, supporting the belief that the liver and bone behave as if they are hyperthyroid in untreated Allan–Herndon–Dudley patients.

Conclusions

Based on an estimate that 10% of males with developmental psychomotor retardation have X-linked mental retardation (XLMR), finding 2 patients out of about 500 institutionalized men with clinically significant mutations in MCT8 indicates that about 4% of patients with XLMR have MCT8 mutations. "Block and replace" treatment with L-T_4 plus PTU normalized the thyroid-function tests, but clinical responses were meager in an adult patient with a 3-base-pair deletion mutant.

ANALYSIS AND COMMENTARY

It is not clear from the text whether rT_3 levels were low in any of the eight patients, or whether any patients were taking thyroid medication, or drugs like carbamazepine, which can increase the T_3:rT_3 ratio and decrease the free T_4 level (2). It is difficult to establish which men with retarded psychomotor development have X-linked mental retardation. The estimate of 10% used by the authors is crucial for their estimate that 4% of patients with XLMR have MCT8 mutations: some other studies indicate the prevalence of MCT8 to be about 0.4% in patients with XLMR (1).

Attempting to treat patients with Allan–Herndon–Dudley by raising thyroid hormone levels in the hope that other thyroid hormone transporters (such as MCT10, organic anion transporter peptides [OATPs], and L-type amino acid transporters) would compensate for the loss of MCT8 activity did not cause much clinical improvement, and resulted in further weight loss. The current study with PTU combined with T_4 did normalize thyroid function, but it produced only minor clinical responses, similar to those previously reported in a 16-year-old boy (3).

Diiodothyropropionic acid (DITPA) is a weak agonist for both the alpha and beta thyroid hormone receptors, and it does not appear to depend on MCT8 for entry into cells. There is a new report on the use of DITPA for several years in four young children with MCT8 mutations, starting at the age of 8 to 25 months (4). Treatment with a combination of PTU plus L-T_4 had been tried previously in three of the children: one developed hypogranulocytosis (4). DITPA normalized the elevated serum T_3 and TSH levels, and raised T_4 and rT_3 levels into the borderline-low range. SHBG levels and sleeping heart rates improved in all four children, two gained weight, and all four showed a transient increase in skeletal muscle–derived creatine kinase. Although MCT8 knock-out mice have negligible neurologic impairment, some cerebral markers suggestive of hypothyroidism improved after giving them DITPA. Unfortunately, DITPA produced little improvement of psychomotor development in these children. It seems that therapy would need to be begun in early pregnancy to overcome the severe defects in central nervous system (CNS) development, but it would also be important that any thyroid analog that would be used prenatally would respond appropriately to CNS deiodinases, which are important for protecting cells from premature neuronal maturation.

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Valproic Acid Therapy Causes Subclinical Hypothyroidism in Children with Epilepsy

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Kim SH, Chung HR, Kim SH, Kim H, Lim BC, Chae JH, Kim KJ, Hwang YS, Hwang H. Subclinical hypothyroidism during valproic acid therapy in children and adolescents with epilepsy. Neuropediatrics 2012;43:135-9. Epub May 22, 2012; doi: 10.1055/s-0032-1313913.

SUMMARY

Background

Anticonvulsants have been responsible for alterations of thyroid function in several ways. In patients with hypothyroidism who are undergoing levothyroxine therapy, phenobarbital and carbamazepine can accelerate the degradation and increase the dose requirement for L-T_4. Diphenylhydantoin may interfere with thyroxine binding to binding proteins and thereby reduce T_4 levels. The current report is a study of the effect of valproic acid on thyroid function in children with epilepsy.

Methods

The investigators studied 61 ambulatory children with epilepsy who had taken valproic acid (VPA) for more than 6 months, who had normal school function, normal MRI images, good seizure control, and absence of systemic disorders. For controls, they studied 144 age- and sex-matched children who visited the outpatient clinic during the same period at the Pediatric Department of Seoul University. Patients and controls each had thyroid-function tests and had follow-up tests on the same dose of valproic acid if an abnormality was found. Patients with abnormal tests were referred to a pediatric neurologist. Thyroid tests included measurement of TSH, FT_4, total T_3, and anti-TPO. Serum valproic acid was also measured.

Results

The mean age of the children was 10 years. The mean TSH in the VPA group was higher than that in the control group (4.6 vs 2.7 mU/L, $P<0.01$); FT_4 was slightly higher and T_3 slightly lower in the VPA group as compared with the controls. None of the children had positive anti-TPO. TSH >4 mU/L was found in 52% of the VPA group as compared with 17% of controls ($P<0.001$); TSH >10 mU/L was found in 8.2% of the VPA group as compared with none of the controls ($P<0.001$). No clinical features of hypothyroidism were found in the evaluation by the endocrinologist.

On follow-up, 61.5% (16 of 26) of patients exhibited a persistently elevated TSH level. When eight patients with subclinical hypothyroidism underwent follow-up thyroid-function tests 3 months after discontinuing VPA therapy, seven showed a decrease in TSH level to the normal range. The serum valproate level was significantly higher in the 32 children with subclinical hypothyroidism than in the 29 with normal TSH (97.4±35.8 vs. 70.6±29.4 µg/ml, $P<0.005$) and the VPA dose was greater (25±6 mg vs. 20±5 mg/kg/day, $P<0.001$).

Conclusions

Subclinical hypothyroidism is prevalent among children with epilepsy on VPA therapy. This seems to justify screening for thyroid dysfunction during VPA therapy, especially when a high dose of VPA is used.

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ANALYSIS AND COMMENTARY

The 50% frequency of slightly elevated serum TSH in patients taking valproic acid is higher than the 26% reported this year in a study of 57 Indian children taking this anticonvulsant (1). More importantly, subclinical hypothyroidism, with TSH >10 mU/L, occurred in 8.2% of patients in the current study, but no treatment for subclinical hypothyroidism was recommended. If one were to apply conservative recommendations for adults with this degree of subclinical hypothyroidism, the children would have been treated with levothyroxine (2).

Although valproic acid has been used for the treatment of epilepsy for over 40 years, its mechanism of action is still unclear; this is also the situation with regard to the basis for the elevation of serum TSH. Valproic acid could increase serum TSH by affecting the complex central neuroendocrine control of TSH release that in turn might elevate serum FT_4. Unfortunately, the serum FT_4 was not reported in the patients with either degree of elevated serum TSH. However, if the TSH elevation persisted with higher FT_4, there would be suppression feedback to reduce the serum TSH level. Valproic acid also inhibits histone deacetylase, so it can modify transcription of many genes. The pathophysiology of the TSH elevation requires further investigation, as does the treatment of the subclinical hypothyroidism in these children.

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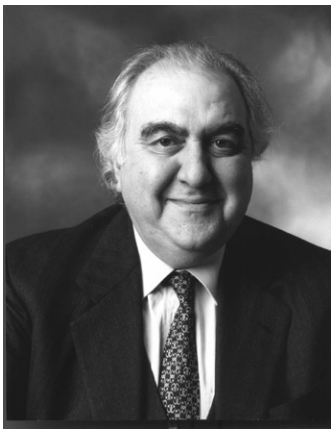
IN MEMORIAM

Professor Aldo Pinchera (1934–2012)



Professor Aldo Pinchera passed away on the 11th of October 2012 at the age of 78. Italian Endocrinology lost a great mentor, one of the founders of Endocrinology in Italy and one of its greatest ambassadors in the world.

Aldo Pinchera graduated from the University of Rome in 1958, obtained the post-graduate degree in Endocrinology and Metabolic diseases from the same University in 1961, and the Doctorate in Endocrinology in 1967. After training in several foreign institutions, such as the University of Marseille, the University of Barcelona, the Massachusetts General Hospital, Harvard Medical School, the Massachusetts Institute of Technology, he then moved to Pisa, where in 1980 he became Professor of Endocrinology until his retirement in 2009. He was then appointed Emeritus Professor of the University of Pisa. From 1981 to 2009 he directed the Post-graduate school in Endocrinology and Metabolic diseases at the University of Pisa. Among his numerous academic positions, Aldo Pinchera was Vice-President of the National University Council from 1998 to 2008. Throughout his career, he received numerous awards from the most important scientific institutions in the world. The most recent prize was the prestigious Lissitzky Career Award he received in Pisa during the last annual meeting of the European Thyroid Association. Aldo Pinchera has been President (and Honorary Member) of the European Thyroid Association, President of the Italian Association of the Thyroid, Regional Coordinator for West Central Europe and member of the Board of the International Council for Control of Iodine Deficiency Disorders, Member of the European Commmunity Thyroid Experts Panel for the consequences of the Chernobyl accident.

Aldo Pinchera had a wide editorial activity. He founded and directed for many years the international Journal of Endocrinological Investigation, official journal of the Italian Society of Endocrinology, and the national journal, l'Endocrinologo. He served in the Editorial Board of all the major international journals in the field of Endocrinology and Metabolism. His scientific interests ranged from thyroid diseases, with particular regards to thyroid autoimmunity, thyroid cancer and endemic goiter, to parathyroid diseases and calcium metabolism, to obesity. His scientific activity translated into the publication of more than 630 peer-reviewed papers in international journals, 10 international volumes as Editor or Co-Editor, 36 chapters in international textbooks.

Moved by his insatiable desire to bring endocrine research forward through the creation of a solid international network, Aldo Pinchera, a bright and keen investigator, selected and grew up a number of capable fellows, thus creating the Pisan Endocrinology School, one of the strongest in Italy. Many of his pupils have reached positions as full professors in several Universities in Italy, after spending long periods of research and training in prestigious institutions abroad. He has been inspirational for generations of your researchers. His intelligence and his drive were contagious for young (and less young) fellows in Pisa and throughout Italy. His wisdom represented a reference point for a good advice or suggestion in troubled times or difficult situations. We cannot believe that we cannot give him a call any longer to discuss any kind of issue with him.

We miss Aldo and will continue to miss him. We have lost our Mentor. The Endocrine Community has lost one of the giants in this field. His achievements will continue to live after his death. He will live in our hearts forever.

Luigi Bartalena, Luca Chiovato, Gianfranco Fenzi,
Claudio Marcocci, Stefano Mariotti,
Enio Martino, Furio Pacini, Paolo Vitti,
on behalf of all of Aldo Pinchera'a pupils

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