Serum Thyrotropin Concentration in Children with Isolated Thyroid Nodules

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Objective To investigate the correlation between serum thyroid-stimulating hormone (TSH) concentration and nodule nature in pediatric patients with thyroid nodules, with the aim of identifying a marker able to differentiate benign and malignant nodules.

Study design This was a retrospective analysis of serum TSH concentrations in a multicentric case series of 125 pediatric patients with benign and malignant thyroid nodules.

Results Of the 125 patients, 99 had benign thyroid nodules and 26 had differentiated thyroid cancer (24 papillary and 2 follicular). Final diagnosis was based on surgery in 57 cases and on a benign cytology plus clinical follow-up in 68 cases. Serum TSH concentration was significantly higher in patients with thyroid cancer compared with those with benign nodules (3.23 ± 1.59 mU/L vs 1.64 ± 0.99 mU/L; $P < .001$). Binary logistic regression analysis revealed that serum TSH was the sole predictor of malignancy ($P < .001$). Dividing the patient cohort into 5 groups based on serum TSH quintiles (TSH cutoffs 0.40, 1.00, 1.50, 1.80, and 2.80 mU/L), we observed that cancer prevalence increased in parallel with serum TSH ($P < .001$), with respective rates of 0%, 4%, 16%, 32%, and 52% in the 5 quintile groups.

Conclusion Because cases with malignant nodules are most likely seen in the upper normal serum TSH range (ie, >2.8 mU/L), serum TSH concentration can serve as a predictor of thyroid cancer in pediatric patients with thyroid nodules and can inform the decision of when to submit patients to further investigation by cytology. *(J Pediatr 2013;163:1465-70)*.

Thyroid cell proliferation depends on thyrotropin (thyroid-stimulating hormone [TSH]), which is the main factor acting on thyroid tissue. Evidence suggests that TSH signaling may be implicated in differentiated thyroid cancer, in which malignant cells usually express TSH receptor.[1] Overactivation and hyperfunction of the TSH receptor has been observed in differentiated thyroid cancer, whereas it is most often silenced in the undifferentiated form.[2] Moreover, in animal models, induced TSH elevation leads to thyroid hyperstimulation, resulting in hyperplasia and increased cancer development rate.[3-5]

Clinical observations point to a correlation between thyroid cancer and serum TSH concentration. Several previous investigations of adults with thyroid nodules have shown that a TSH concentration in the upper end of the reference range is correlated with an increased likelihood of thyroid cancer; serum TSH concentrations are higher in patients with differentiated thyroid cancer compared with those with benign thyroid nodules.[6] In addition, patients with nodular goiter have lower serum TSH concentrations and a lower frequency of papillary thyroid cancer when treated with levothyroxine.[7] Moreover, levothyroxine administration at dosages that induce serum TSH suppression have been linked to a reduced risk of thyroid cancer recurrence and increased survival.[8] Finally, levothyroxine treatment may interfere with growth and formation of nodules.[8-12]

Two systematic reviews examining the association between serum TSH concentrations and differentiated thyroid cancer in adults have been published.[13,14] Thyroid nodules are very rare in the pediatric population, with an estimated prevalence of only 0.05%-1.8%,[15,16] and only 1 study to date has investigated this association in children.[17] Furthermore, pediatric thyroid cancer appears to be unique, differing from the adult form in terms of epidemiology and natural history. Thyroid nodules are more often malignant in children than in adults (20%-25% of cases vs 5%-10%),[18-22] and pediatric thyroid cancer is almost invariably well differentiated and thus likely to be TSH-dependent.

In the present study, we investigated the correlation between serum TSH concentration and cytotype/histotype of thyroid nodules in children, with the aim of identifying a biochemical marker of malignancy for use in clinical practice.

BMI	Body mass index
FNAB	Fine-needle aspiration biopsy
TSH	Thyroid-stimulating hormone

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Methods

In this multicenter retrospective study of 125 patients with thyroid nodules diagnosed in childhood or adolescence, data were collected from a series of consecutive cases diagnosed and followed-up between 2006 and 2012 in 9 centers in the Study Group for Thyroid Diseases of the Italian Society for Pediatric Endocrinology and Diabetology. All of the clinicians involved were pediatric endocrinologists working in clinics dedicated to the diagnosis and treatment of thyroid cancer, thyroid nodules, and other complex thyroid disorders. Institutional Review Board approval and patiental informed consent were not required by the institutions for retrospective studies involving the anonymous review of medical records of patients followed at those institutions.

We collected data from patients aged <18 years with thyroid nodules diagnosed by physical examination and thyroid ultrasonography and with a histological diagnosis when submitted to surgery or a cytological diagnosis when submitted to fine-needle aspiration biopsy (FNAB). Patients submitted to FNAB but not to surgery because of benign cytology were followed for at least 1 year, with clinical and echographic evaluation every 6 months to further substantiate the benign nature of the nodule. Inclusion criteria were: (1) largest nodule diameter at least 1 cm and (2) serum TSH and free thyroxine levels measured within the 3 months before FNAB or surgery. The referring clinicians were asked to apply the following exclusion criteria: (1) cases treated for any other childhood cancer or exposed to radiation before the diagnosis of thyroid nodules (n = 32); (2) cases with autoimmune thyroiditis confirmed by thyroid antibody detection or an ultrasound pattern consistent with thyroiditis (inhomogenous and hypoechogenic) (n = 79); (3) cases in which levothyroxine was administered before nodule diagnosis (n = 11); (4) cases with hyperthyroidism (defined as TSH <0.4 mU/L) or under methimazole/propylthiouracil treatment (n = 4); (5) cases with hypothyroidism (defined as low serum free thyroxine concentrations with a concomitant rise in TSH) (n = 9); and (6) cases with a definite histological/cytological diagnosis of thyroid abscess, medullary thyroid cancer, or a rare thyroid histotype (eg, Hurtle-cell adenoma/carcinoma) (n = 6).

Overall, 125 patients (105 females, 20 males) were included in this study. The cytological results yielded by FNAB were classified according to accepted guidelines.[23,24]

Body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters. Published Italian standards for sex- and age-specific BMI percentiles were used to classify patients aged 2-18 years as overweight (85th-95th percentile) or obese (>95th percentile) and to calculate the respective BMI SDS.[25] Patients aged <2 years with weight-for-length >95th percentile were classified as obese.

Serum TSH concentration was measured by highly specific chemiluminescent immunoassays (Roche Diagnostics, Manheim, Germany) in the laboratories of the various centers involved in the study, with intra-assay and interassay variations <10%. TSH reference values were 0.40-4.40 mU/L in all 9 laboratories.

Continuous variables are expressed as mean ± SD (median, range). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the parametric or nonparametric distribution of the numerical variables. The Student *t* test and Wilcoxon and Mann-Whitney tests were used to check between-group differences in variables with a normal distribution and in variables with a skewed distribution, respectively. Pearson correlation coefficients were applied to check univariate associations. The χ^2 test and Fisher exact test were used to assess the distribution of cathegorical variables. Binary logistic regression analysis was used to evaluate the independent influence of factors on the final diagnostic outcome (benign vs malignant), including largest nodule diameter, number of nodules (solitary nodules vs multinodular thyroid disease), age, sex, and serum TSH concentration at the time of FNAB.

Calculations were considered statistically significant at a P value <.05. SPSS version 15.0 (IBM, Armonk, New York) was used for all statistical analyses.

Results

Of the 125 patients in our study cohort, 57 were submitted to surgery based on an FNAB result indicative of malignant or suspicious nodule or despite a benign cytology, clinical/echographic features suggestive of a malignancy (eg, palpable lymph nodes, microcalcifications, intranodular blood flow, ultrasonography-detected lymph node alterations, hypoechogenicity, irregular margins). Cytology was benign in 86 patients (18 who underwent surgery with a final diagnosis of goitrous nodule), malignant in 24 patients (all with histologically confirmed papillary cancer), suspicious in 15 patients (all who underwent surgery, 2 with a final diagnosis of follicular carcinoma, 6 with follicular adenoma, and 7 with benign goitrous nodule). Overall, 26 patients (20.8%) were diagnosed with malignant thyroid nodules based on histology, 24 with papillary carcinoma and 2 with follicular carcinoma. The other 31 patients who underwent surgery received a final diagnosis of benign thyroid nodules with histology demonstrating goitrous nodule (n = 25) or follicular adenoma (n = 6).

In 68 patients, surgery was not performed because the nodule was considered benign. These patients (all with benign FNAB findings) were followed for a mean of 2.3 ± 1.6 years (median, 2.8 years; range, 1.3-6.2 years) with clinical, laboratory, and echographic evaluation every 6 months. Over the follow-up period, no nodule developed suspicious features for malignancy, and thus none of these patients underwent surgery.

Concordance between cytology and histology was seen in all the patients with benign and malignant cytology, and considering the "suspicious" cytology results as malignant,