Differentiated Thyroid Cancer in Children: Prevalence and Predictors in a Large Cohort with Thyroid Nodules Followed Prospectively

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We retrospectively analyzed the findings of a prospective cohort of 75 children referred for thyroid nodules between 2008 and 2013. Prevalence of papillary differentiated thyroid carcinoma was 18.7%. Thyrotropin >2.5 mIU/L, multinodular goiter, solid nodules, irregular margins, and pathologic lymphadenopathies were identified as independent predictors of malignancy. *(J Pediatr 2015;167:199-201).*

Thyroid nodules in children and adolescents have an estimated prevalence of 0.05 to 1.8%.[1] Malignancy risk (MR) in this age group is greater than in adults.[1-7] The management of pediatric thyroid nodules is mainly based upon the adult experience. The main goal of this study is to report our experience in the characterization and management of a prospectively and uniformly followed large cohort of pediatric patients with thyroid nodules in a single tertiary care center and to highlight the findings of each diagnostic tool likely to differentiate benign from malignant thyroid nodules.

Methods

We prospectively studied 75 patients under 19 years of age with thyroid nodules referred to the Division of Endocrinology between 2008 and 2013, who reached a final diagnosis (benign vs malignant) by surgery (n = 62) or by at least 2 years (range 2.5-6.1) of clinical follow-up (n = 13). Sex, age, pubertal status, risk factors (family history of differentiated thyroid cancer, radiation exposure, and previous/coexisting thyroid disease), nodule characteristics, and cervical adenopathies were recorded. Thyroid function was assessed in 62 patients without levothryoxine treatment by thyrotropin, thyroxine, and free thyroxine by electro-chemiluminescence immunoassay (Roche Diagnostics GMBH, Mannheim, Germany) and anti-thyroid antibodies by Immulite (Immulite; Siemens Healthcare Diagnostics Products Ltd, Gwynedd, United Kingdom). Cervical Doppler-ultrasound was performed in all patients recording thyroid nodules characteristics (number, diameter, echoic pattern, margins, calcifications, and vascularization) and the presence of abnormal cervical adenopathies (rounded shape, irregular margins, increased size, absence of hilum, heterogeneous pattern, cystic areas, calcifications, or diffuse/irregular vascularity). All patients underwent ultrasound-guided fine needle aspiration biopsy (FNAB), analyzed by the same cytopathologist and categorized according to the Bethesda System for Reporting Thyroid Cytopathology.[8] Surgery was indicated according to the following criteria: (1) FNAB Bethesda (B) III-VI (n = 26); (2) benign FNAB (B II), persistent or growing thyroid nodules, and risk factors or suspicious ultrasound findings (n = 23); and (3) repeated nondiagnostic FNAB (B I) and risk factors and/or suspicious ultrasound findings and/or persistent or growing thyroid nodules on follow-up (n = 13). Patients with B VI, multinodular goiter, or malignant intraoperative frozen section underwent total thyroidectomy (n = 24), otherwise a lobectomy was performed (n = 38). Retrospectively, the differences between characteristics of benign and malignant thyroid nodules were analyzed. This study was approved by the Institutional Review Board.

Statistical analysis was performed by Student *t* test and χ^2 test. Univariate and multiple binary logistic regression analyses were used to evaluate the independent influence of age, sex, pubertal status, goiter type, thyroid antibodies, and thyrotropin as continuous variable and within designated ranges (cutoffs: 0.5, 1.4, 2.5, 5, and 10 mIU/L) on the final outcome (differentiated thyroid carcinoma). *P* value of <.05 was considered significant. All analyses were performed with SPSS 18.0 (SPSS Inc, Chicago, Illinois) and InfoStat (Universidad Nacional de Córdoba Córdoba, Argentina). MR was calculated for each B category in the operated group. In those patients with diagnostic cytology (B II-VI, n = 49), we analyzed the predictive value of having cancer when results of ultrasound-guided FNAB were B V-VI. Sensitivity, specificity, positive and negative predictive value (PPV/NPV), and diagnostic efficiency were calculated.

B	Bethesda
FNAB	Fine needle aspiration biopsy
MR	Malignancy risk
NPV	Negative predictive value
PPV	Positive predictive value

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Results

Histology is shown in Table I. One-half of the surgically treated thyroid nodules were tumors; papillary differentiated thyroid carcinoma was the only malignant lesion found (22.6%). Table II shows the results of the retrospective evaluation. The finding of palpable cervical adenopathy was the only significant clinical difference. Differentiated thyroid carcinoma presented mainly as a palpable nodule, but 4 out of 7 patients presented with nonpalpable thyroid nodules. Patients with differentiated thyroid carcinoma showed a significantly greater median thyrotropin (2.7 vs 2.2 mIU/L, $P = .04$). The likelihood of differentiated thyroid carcinoma increased with higher thyrotropin concentration, even within normal thyrotropin range (χ^2 98.6%): 7.7% (1/13) for thyrotropin 0.5-1.39 mIU/L, 17.4% (4/23) for thyrotropin 1.4-2.49 mIU/L, 29.4% (5/17) for thyrotropin 2.5-4.99 mIU/L, and 66% (2/3) for thyrotropin 5-10 mIU/L. Multiple binary logistic regression analysis found significantly increased ORs for thyrotropin >2.5 mIU/L (OR 6.5, 95% CI 1.04-40.7; $P = .04$) and for multinodular goiter (OR 10.4, 95% CI 1.97-55; $P < .006$). Ultrasound findings of a solid nodule with irregular margins and pathologic cervical adenopathies were significantly associated with malignancy. MR for each B category was as follows: 15.4% B I, 4.3% B II, 14.3% B III, 0% B IV, 50% B V, and 100% B VI. B V and VI FNAB results showed a PPV and NPV for malignancy of 75% and 92%, respectively, with sensitivity of 75%, specificity 92%, and diagnostic efficiency of 89%.

Discussion

The observed prevalence of differentiated thyroid carcinoma of 18.7% (14/75 patients) is in line with previous reports.[1,3-7] Even when the surgery rate was high (82%), one-half of the operated patients had a tumoral thyroid disease that deserved surgery, 22.6% of which was cancer. There are different reports about the risk of nonpalpable thyroid nodules in adults.[9-11] In our cohort, 3 out of 5 patients with thyroid nodules incidentally found by ultrasound had differentiated thyroid carcinoma. According to this, incidental thyroid nodules in children would deserve the same diagnostic strategy as palpable ones, but recommendations cannot be made due to the small sample size.[12] As in previous reports, our study confirms that a thyrotropin >2.5 mIU/L at presentation is an independent predictor of differentiated thyroid carcinoma in children.[13,14] Although cervical ultrasound cannot reliably distinguish benign from malignant thyroid nodules, some features are suggestive of malignancy.[15-17] In our cohort, a solid nodule and irregular margins were associated with differentiated thyroid carcinoma. Pathologic adenopathy, either palpable or detected by ultrasound, were always associated with cancer, making their systematic evaluation mandatory. The incidence of differentiated thyroid carcinoma in adult patients with multinodular goiter is reported to be equal or considerably lower than in patients with a single nodule.[18,19] Interestingly, 19 (25%) of our patients had multinodular goiter, 17 underwent surgery, and 7 had cancer, showing a higher incidence of differentiated thyroid carcinoma in multinodular goiter than in single nodules

Table I. Histologic findings

Total	Solitary nodule	Multinodular goiter
n = 62	n = 45	n = 17
Nodular hyperplasia	18	6
Colloid cyst	4	
Intrathyroidal TC	1	
Lymphoepithelial cyst	1	
LT	2	
Multinodular goiter		3
Follicular adenoma	12	1
Papillary carcinoma	7	7

LT, lymphocytic thyroiditis; *TC*, thyroglossal cyst.

Table II. Retrospective evaluation of differences between benign and malignant nodules

	Benign	Malignant	
	61	14	*P* value
Clinical data			
Age (years, median, range)	14 (6.4-19)	13.4 (8.3-16.9)	NS
♀/♂	51/10	9/5	.14
Pubertal	55	10	.08
Risk factors	2	1	NS
Goiter type (physical examination)			
Palpable			
Solitary nodule	45	7	.11
Multinodular goiter	9	3	.68
Nonpalpable			
Diffuse goiter	5	1	NS
Normal thyroid	2	3	.04
Palpable lymph nodes	-	4	<.01
Laboratory*			
Thyrotropin (mIU/L, median, range)	2.2 (0.01-100)	2.7 (1-8.4)	.04
Thyroid function			
Normal	43	10	NS
Hypothyroidism	4	2	.58
Hyperthyroidism	3	-	.62
Thyroid antibodies	12/56	5/13	.28
Ultrasound			
Solitary nodule	49	7	.04
Multinodular goiter	12	7	.04
Greatest diameter (mm, median, range)	22.5 (8-80)	19.1 (8-50)	NS
Solid	27	14	<.01
Irregular margins	2	3	.04
Intranodular microcalcifications	11	5	.16
Increased intranodular flow	24	7	.55
Pathologic adenopathies	-	5	<.01
Cytology			
B I nondiagnostic	17	2	
B II benign	29	1	
B III AUS/FLUS	6	1	
B IV follicular neoplasm	6	-	
B V suspicious for malignancy	3	3	
B VI malignant	-	7	

AUS, atypia of undetermined significance; *FLUS*, follicular lesion of undetermined significance; *NS*, nonsignificant.
*N = 62.

($P = .03$). Even more, the only patient with dyshormonogenesis, known as a predisposing condition for multinodularity, had multiple adenomas.[20] Our region is a mild iodine-deficient area, corrected through the mandatory use of iodized salt, and multinodular goiter is not frequent.[21] An adequate FNAB is a key diagnostic tool, but most patients refused more than 2 punctions. Small nodules (<10 mm), multinodular goiter, or cystic lesions rendered most FNAB inadequate (16/19 B I). In fact, the 2 B I patients with differentiated thyroid carcinoma underwent surgery for clinical changes and/or risk factors. This study is one of the very few cytological reports using the Bethesda System for Reporting Thyroid Cytopathology for FNAB in pediatrics.[22-24] MR in each B category in our group was similar to that reported for adults.[8] Malignancy prediction of the intermediate categories (B III-IV) is troublesome; all the patients within these categories were operated, but only 1 out of 13 had cancer. B V and VI correctly assessed malignancy (NPV 92%). As in other pediatric nodule case series, papillary differentiated thyroid carcinoma was the only malignant finding.[4-7]

Our results confirm a higher prevalence of differentiated thyroid carcinoma in pediatric thyroid nodules than in adults. Any thyroid nodules in pediatrics deserve a complete initial assessment to select adequately patients for surgery. Thyrotropin >2.5 mIU/L, ultrasound signs as a solid nodule, irregular margins, pathologic adenopathies, or multinodular goiter were identified as independent predictors of malignancy together with FNAB results. Future efforts should be directed toward identifying more malignancy predictors in order to reduce the need for surgery. ■

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References

1. Niedziela M. Pathogenesis, diagnosis and management of thyroid nodules in children. Endocr Relat Cancer 2006;13:427-53.
2. Wiersinga WM. Management of thyroid nodules in children and adolescents. Hormones (Athens) 2007;6:194-9.
3. Corrias A, Mussa A, Baronio F, Arrigo T, Salerno M, Segni M, et al. Diagnostic features of thyroid nodules in pediatrics. Arch Pediatr Adolesc Med 2010;164:714-9.
4. Hung W. Solitary thyroid nodules in 93 children and adolescents: a 35-year experience. Horm Res 1999;52:15-8.
5. Mirshemirani A, Roshanzamir F, Tabari AK, Ghorobi J, Salehpoor FA. Thyroid nodules in childhood: a single institution experience. Iran J Pediatr 2010;20:91-6.
6. Khozeimeh N, Gingalewski C. Thyroid nodules in children: a single institution's experience. J Oncol 2011;2011:974125.
7. Gupta A, Ly S, Castroneves LA, Frates MC, Benson CB, Feldman HA, et al. A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. J Clin Endocrinol Metab 2013;98:3238-45.
8. Cibas E, Ali S. The Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol 2009;132:658-65.
9. Papini E, Guglielmi R, Bianchini A, Crescenzi A, Taccogna S, Nardi F, et al. Risk of malignancy in nonpalpable thyroid nodules: predictive value of ultrasound and color-Doppler features. J Clin Endocrinol Metab 2002;87:1941-6.
10. Hagag P, Strauss S, Weiss M. Role of ultrasound-guided FNAB in evaluation of nonpalpable thyroid nodules. Thyroid 1998;8:989-95.
11. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 1997;126:226-31.
12. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al., ATA Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised ATA management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
13. Chiu HK, Sanda S, Fechner PY, Pihoker C. Correlation of TSH with the risk of paediatric thyroid carcinoma. Clin Endocrinol (Oxf) 2012;77:316-22.
14. Mussa A, Salerno MC, Bona G, Wasniewska M, Segni M, Cassio A, et al. Serum TSH concentration in children with isolated thyroid nodules. J Pediatr 2013;163:1465-70.
15. Corrias A, Einaudi S, Chiorboli E, Weber G, Crinò A, Andreo M, et al. Accuracy of FNAB of thyroid nodules in detecting malignancy in childhood: comparison with conventional clinical, laboratory and imaging approaches. J Clin Endocrinol Metab 2001;86:4644-8.
16. Wienke JR, Chong WK, Fielding JR, Zou KH, Mittelstaedt CA. Sonographic features of benign thyroid nodules interobserver reliability and overlap with malignancy. J Ultrasound Med 2003;22:1027-31.
17. Kim EK, Park CS, Chung WY, Oh KK, Kim DI, Lee JT, et al. New Sonographic criteria for recommending FNAB of nonpalpable solid nodules of the thyroid. AJR Am J Roentgenol 2002;178:687-91.
18. McCall A, Jarosz H, Lawrence AM, Paloyan E. The incidence of thyroid carcinoma in solitary cold nodules and in MNG. Surgery 1986;100:1128-32.
19. Gandolfi PP, Frisina A, Raffa M, Renda F, Rocchetti O, Ruggeri C, et al. The incidence of thyroid carcinoma in MNG: retrospective analysis. Acta Biomed 2004;75:114-7.
20. Papendieck P, Gottlieb S, Gruñeiro-Papendieck L, Papendieck CM, Iotti A, Targovnik H, et al. Multiple follicular adenomas in a girl with congenital hypothyroidism due to a TPO gene mutation. Horm Res Paediatr 2012;78:20.
21. Gruñeiro-Papendieck L, Chiesa A, Mendez V, Bengolea S, Prieto L. TSH neonatal levels as an index of iodine sufficiency. Horm Res 2004;62:272-6.
22. Smith M, Pantanowitz L, Khalbuss WE, Benkovich VA, Monaco SE. Indeterminate pediatric thyroid FNAB: a study of 68 cases. Acta Cytol 2013;57:341-8.
23. Monaco SE, Pantanowitz L, Khalbuss WE, Benkovich VA, Ozolek J, Nikiforova MN, et al. Cytomorphological and molecular genetic findings in pediatric thyroid FNAB. Cancer Cytopathol 2012;120:342-50.
24. Norlén O, Charlton A, Sarkis LM, Henwood T, Shun A, Gill AJ, et al. Risk of malignancy for each Bethesda class in pediatric thyroid nodules. J Pediatr Surg 2014. In press.