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A case series and review on pediatric thyroid nodules

Abstract

Thyroid nodules have a higher risk of malignancy in children and hence need close monitoring. Primary care providers often obtain the initial thyroid work up. Once there patients are referred to specialists, primary providers are unsure about subsequent management and follow up. We present here three cases of thyroid nodules with different initial presentation, diagnosis and management. This article provides a good brief summary about thyroid nodule and reiterates the importance of long term follow up of these patients by primary care provider and endocrinologists.

Keywords: thyroid nodules, thyroid cancer, pediatrics

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Abbreviations: DTC, differentiated thyroid cancer; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma, MTC, medullary thyroid carcinoma; ATA, american thyroid association; PTMC, Papillary thyroid micro carcinoma

Introduction

Parents often bring their children to the Pediatrician's office with concerns about possible thyroid dysfunction. Often an online search or social media posts suggest that thyroid conditions can be the cause of a plethora of nonspecific complaints such as excessive weight gain, fatigue, irregular menstrual periods and behavioral problems. Parents who are anxious to find an explanation for their child's issues often seem almost hopeful that a treatable thyroid condition might be the answer that they are seeking. Other families have concerns about a strong family history of thyroid disease or other autoimmune conditions. For these reasons, simple thyroid lab testing is commonly ordered to address these concerns. Generally, when thyroid function testing shows abnormalities or when a goiter is noted on exam, additional testing is performed which often includes a thyroid ultrasound. Children who are found to abnormal lab or imaging results are often referred to Pediatric Endocrinologists. This article focuses on the evaluation of children who are found to have thyroid imaging which indicates the presence of a single or multiple thyroid nodules. An outline for approach and management of thyroid nodules in children is presented.

Illustrative cases

This case series report 3girls who had thyroid nodules but with different initial presentations, diagnosis and management (Table 1).

First case is a 12year old African American girl who presented with goiter. She had negative autoimmune thyroid disease or family history of thyroid disease. On exam, she had goiter, a nodule felt on right thyroid lobe with no lymphadenopathy. She had normal thyroid labs. Biopsy of nodule resulted follicular lesion of undetermined significance. She underwent right thyroid lobectomy and final pathology was follicular adenoma.

Second case is a 12-year-old White girl who presented with weight gain. Her mother and grandmother had hypothyroidism. She was started on levothyroxine due to Hashimotos hypothyroidism. On exam, she had goiter but no nodules felt. Initial ultrasound did not show nodules but repeat did and biopsy confirmed papillary thyroid carcinoma. She underwent total thyroidectomy with paratracheal lymph node dissection. Her iodine uptake scan was negative for uptake and currently continuing levothyroxine replacement and close monitoring of thyroglobulin levels.

Third, is an African American 17year old girl who presented with headache. She had no autoimmune thyroid disease or family history of thyroid disease. She had normal thyroid exam but TSH was suppressed with normal free T4 but elevated T3 levels. Her thyroid ultrasound showed a nodule with increased iodine uptake. She underwent left thyroidectomy for large toxic adenoma.

Discussion

Palpable thyroid nodules are less common in children than adults but sonographic and or pathological abnormalities are common (0.2–5% of children, 13% of adolescents).[1] Non palpable thyroid nodules detected by imaging have the same risk for differentiated thyroid cancer (DTC) as a palpable thyroid nodules of similar size.[2] The risk for malignancy in thyroid nodules in children is higher at 22-26% as compared to 7-15% in adults.[3] Survival from pediatric thyroid cancer is excellent, with reported 30-year survival rates of 99% to 100% and 91% for papillary and non-papillary thyroid carcinoma, respectively.[4]

Differential diagnosis for thyroid nodules includes benign (75%) and malignant causes (25%). Benign nodules include colloid or adenomatoid nodule, follicular or Hurthle cell adenoma, and simple cyst (which are lined by benign epithelial cells). Malignancy affecting thyroid nodules are papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and medullary thyroid carcinoma (MTC). Poorly differentiated variants and anaplastic thyroid carcinomas are rare in children.

The risk factors for thyroid nodules in children are listed in Table 2.[5] Though the risk for cancer is 2.5fold higher with a family history of benign thyroid disease and 4fold higher with a family history of thyroid cancer, a routine neck palpation by an experienced provider might be sufficient monitoring. According to Bauer et al, an ultrasound should be performed if the gland feels suspicious or if there is a high

risk family history. American Thyroid Association (ATA) guidelines recommend ultrasound with autoimmune thyroiditis only if there is a suspicion about a nodule or abnormal lymphadenopathy on physical examination.

An initial evaluation, management and follow up for a thyroid nodule is shown in Figure 1. The following recommendations are mostly adapted from American Thyroid Association (ATA) guidelines published in 2015.[6]

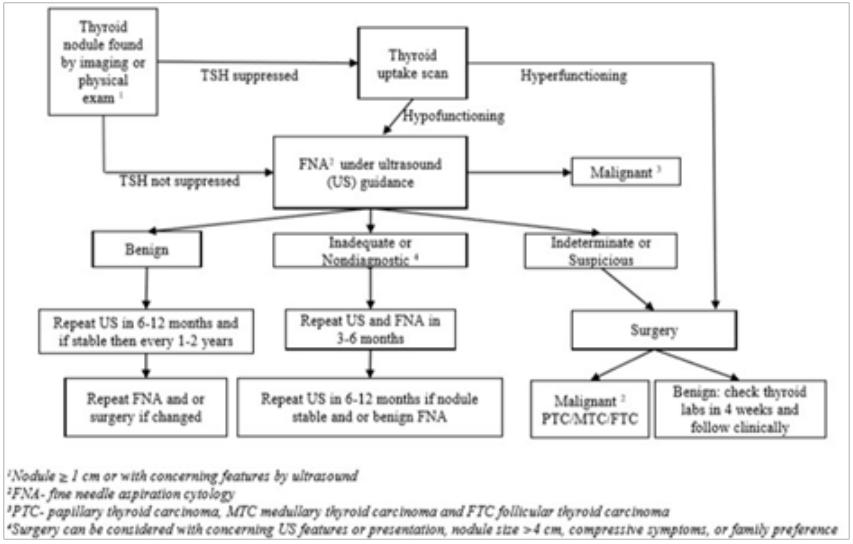

Figure 1 Initial evaluation, treatment, and follow up of the pediatric thyroid nodule.

Ultrasound features

Nodular characteristics and clinical context should be used to identify the need for FNA. Features such as hypo echogenicity, irregular margins, increased intranodular blood flow, presence of microcalcifications, and abnormal cervical lymph nodes are more common in malignant lesions. Ultrasound guided fine needle aspiration (FNA) should be performed if thyroid nodule is more than 10mm, unless purely cystic and for nodules 5-10mm with suspicious features.[6]

Cytopathology findings

These are categorized according to The Bethesda System for Reporting Thyroid Cytopathology. In this six-tier system, FNA results are reported as

a. Nondiagnostic or unsatisfactory;
b. Benign;
c. Atypia or follicular lesion of undetermined significance;
d. Follicular/Hurthle neoplasm or suspicious for follicular/Hurthle neoplasm;
e. Suggestive of malignancy;
f. Malignant.[7]

Due to increased probability of malignancy among indeterminate categories in children, a lobectomy plus isthmusectomy is recommended.

Follow-up of benign cytology should be risk stratified according to risk factors as well as the ultrasound features. Highly suspicious thyroid nodules in children should be removed despite benign cytology. Thyroid nodules with low to intermediate suspicion should undergo repeat ultrasound at 12months but delaying surveillance up to 24months may be reasonable in large, predominantly cystic nodules.[8]

Need for thyroid replacement with nodules

There are data supporting the efficacy of thyroid replacement therapy to reduce the size and risk of subsequent nodule formation, but there are no data to weigh this potential benefit against the potential risks of long-term suppression therapy.

In patients with compressive symptoms or a history of radiation exposure the benefits of thyroid replacement therapy may be more apparent.

Nodules with suppressed TSH

If nodule is associated with a suppressed TSH, a thyroid scintigraphy should be pursued. Increased uptake within the nodule is consistent with autonomous nodular function. Surgical resection, most commonly lobectomy, is the recommended approach for most autonomous nodules in children and adolescents.

Benign lesions

These should be followed by serial ultrasound and undergo repeat FNA if suspicious features develop or the lesion continues to grow. Indications for surgery are as described above in Figure 1.

Cystic lesions

FNA should be considered for lesions that have more than 50% solid component, if the solid component has concerning ultrasound features, or if there are abnormal cervical lymph nodes. For children with large cystic lesions, lobectomy may be reasonable based on symptoms or for cosmetic purposes.

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Table 1 Illustrative cases

	Case 1	**Case 2**	**Case 3**
Age	12	12	17
Sex	Girl	Girl	Girl
Ethnicity	African American	White	African American
Chief Complaint	**Goiter**	**Weight gain**	**Headache**
Thyroid symptoms	None	Rest negative	None
Family history of thyroid disease	Negative	Mother & grandmother with hypothyroidism	Negative
Autoimmunity	Negative	Hashimotos +	Negative
Vitals (heart rate &blood pressure)	Normal	Normal	Mild tachycardia
Physical Examination	Goiter, nodule on right side non tender	Goiter, no nodules	Normal thyroid exam
Lymphadenopathy neck	None	Upper cervical	None
Labs	Normal TSH[1] and	Elevated TSH at 153 low free T4 at 0.1	Low TSH 0.01
Free T4(0.9-1.6ng/dl)	Free T4		Free T4 1.4
			T3 2.19(0.8-2ng/ml)
Thyroid replacement medication	Not started	Synthroid 112mcg once daily	None
Ultrasound Thyroid (dimensions in cm)	Right lobe:	Right lobe: 7.4x3.6x3.6	Right lobe:
	5.58x3.29x4.3	Left lobe:	4.17x1.33x1.10
	Nodule right side: 5.0x3.8x3.1	7.5x3.6x3.2	Left lobe:
	Left lobe:	Isthmus:1.5	5.64x2.17x2.22
	4.7x1.1x1.2		Nodule Left:
			3.50x2.27x2.53
Nodule features	Solid and isoechoic	Very hyper vascular Coarse calcifications+ No focal nodule	Solid hyperechoic, heterogeneous nodule with internal vascularity
		LN[2] 1.7-2cm bilaterally Repeat in 6months showed nodule 1.8cm right side.	
FNA[3] Thyroid and Pathology report	Follicular lesion of undetermined significance	Papillary thyroid carcinoma	Indeterminate
Other imaging	None	CT neck and chest: no concerning pulmonary or neck LN	I-123[4] uptake with increased uptake in left lobe and suppression in right lobe.
Treatment	Right thyroid lobectomy	Total thyroidectomy with dissection of para tracheal LN	Left thyroidectomy
Final Pathology	Follicular adenoma	Papillary thyroid cancer T1N0- low risk	Large toxic adenoma
Post-surgery labs	Normal thyroid, calcium and PTH[5]	Restarted Synthroid	Normal thyroid labs
		Normal calcium, PTH	
Follow up		I-123 scan- no uptake	
		Thyroglobulin 0.1	

[1]TSH- thyroid stimulating hormone (0.5-4.5mcIU/ml);
[2]LN- lymph nodes;
[3]FNA- fine needle aspiration;
[4]I-123- iodine 123 isotope;
[5]PTH- parathyroid hormone.

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Table 2 The risk factors for thyroid nodules in children[5]

1	Family history of thyroid nodules or thyroid cancer
2	Iodine deficiency
3	Radiation exposure especially in childhood cancer survivors
4	History of thyroid disease like autoimmunity
5	Elevated serum thyroid stimulating hormone (TSH)
6	Several genetic syndromes like APC associated familial adenomatous polyposis, DICER 1 syndrome, PTEN hamartoma tumor syndrome etc

Multinodular goiter

Each thyroid nodule carries an independent risk for developing differentiated thyroid cancer (DTC). FNA should be performed on any thyroid nodules with suspicious ultrasound features but does not need to be performed on all nodules that have the same ultrasound features.[9]

Papillary thyroid carcinoma

Initial treatment approach for PTC is total thyroidectomy with or without lymph node dissection based on preoperative staging which can include neck ultrasound with FNA of abnormal lymph nodes, serum thyroglobulin and antibody level, chest X-ray, and CT neck and chest with contrast. Utilizing high-volume thyroid surgeons can reduce the rate of complications of thyroidectomy which are transient or permanent hypoparathyroidism (5%–15%), recurrent laryngeal nerve damage, spinal accessory nerve injury, and Horner syndrome (1%–6%) (14). The utility of intact parathyroid hormone level is fairly well established with a level of <10–15pg/mL correlating with an increased risk to develop clinically significant hypocalcemia and thus help to stratify patients who would benefit from more intensive monitoring and treatment with calcium and calcitriol. ^{131}I radioactive iodine ablation therapy is indicated for treatment of persistent local or nodal disease that cannot be resected and for known or presumed distant metastases.

The short-term side effects of ^{131}I are damage to tissues that incorporate iodine, resulting in sialadenitis, xerostomia, dental caries, stomatitis, ocular dryness, and nasolacrimal duct obstruction.[10] In post pubertal males, a transient rise in follicle-stimulating hormone is common and may persist for up to 18months after ^{131}I exposure. Transient amenorrhea and menstrual irregularities are reported in up to 17% of females under the age of 40years.[11] Acute suppression of bone marrow may occur but hematologic parameters usually normalize within 60days after ^{131}I exposure.[12] Unfortunately, there is a lack of long-term data to define a safe activity of^{131}I,

and additional study is clearly warranted to determine the risks for secondary malignancies later in life. There is also an increased risk for pulmonary fibrosis in patients who had pulmonary metastasis and had ^{131}I. Patients with thyroid cancer are categorized into low or intermediate or high risk based on extent of tumor and kept on TSH suppressive therapy using levothyroxine. They are monitored using ultrasound neck, thyroglobulin and anti-thyroglobulin antibody levels.

Papillary thyroid micro carcinoma (PTMC) are defined as lesions with focus of 1cm or less involvement. Lymph node metastases are more common in patients less than 19years of age with PTMC (72.5%) suggesting that they might not be indolent and warrant continued follow-up.

Follicular thyroid carcinoma

FTC currently represents 10% or less of thyroid cancer cases diagnosed in children or young adults and the prevalence appears to be decreasing over time.[13,14] Iodine deficiency is the one clear risk factor for the development of FTC. FNA usually reports as indeterminate result and not sufficient for making the diagnosis of FTC.[15] Patients with clear evidence of vascular invasion, distant metastasis, and/or tumor size >4cm should be treated with total thyroidectomy and with radioactive iodine ablation. In all children diagnosed with FTC, genetic counseling and testing for germline PTEN mutations should be considered.

Medullary thyroid carcinoma

MTC is seen with multiple endocrine neoplasia (MEN) 2 and 3 and associated with RET proto oncogene mutations. Thyroidectomy is done at very early ages of life based on risk level.

Long term follow up

Children with Differentiated Thyroid Cancer (DTC) may experience adverse psychosocial effects and be non-adherent with thyroid replacement therapy. Attention to these possibilities and supportive counseling as required are important adjuncts in the long-term follow-up of children with DTC. Future studies on the impact of a DTC diagnosis and treatment on quality of life in children are required. Recurrence of DTC in children has been reported as long as 40years after initial therapy. For that reason, children with DTC should be followed for life, albeit with decreasing intensity for those with no evidence for disease.

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Conflicts of interest

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