Pediatric Polycystic Thyroid: Rare Innocent Finding or Harbringer of Disease?

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Background: Ultrasound identification of multiple small thyroid cysts in adults, so called polycystic thyroid (PCT) disease has been associated with overt hypothyroidism. The significance of PCT in childhood is unclear.

Methods: We report ultrasound, clinical , biochemical and follow-up data on eight patients (four males and four females, mean age 13.2 years) found to have PCT.

Results: All patients on ultrasound had increased thyroid gland size, with multiple small cysts (<6 mm) throughout the gland, but most often at the periphery, without evidence of vascular changes or echogenicity. With the exception of one patient with initial slight increase of TSH, all patients had normal free T4, TSH, and negative thyroid auto-antibodies. No progression was noted on follow up.

Conclusions: Pediatric PCT is characterized by a benign, asymptomatic presentation . However, as most patients with overt hypothyroidism and PCT have been adults, a longer period of clinical observation in pediatric patients is prudent to ensure that deterioration of thyroid function does not occur over time.

INTRODUCTION

Sophisticated high resolution imaging techniques have become widely available and frequently used. With increased numbers of imaging procedures being done for various indications, there has been a corresponding increased discovery of incidental findings of uncertain pathologic significance that often pose dilemmas for diagnosis, therapy and follow-up. In 2010, Avula et al. in Canada reviewed 256 pediatric neck ultrasounds performed for non-thyroidal indications in which the entire thyroid was visible. They found that 52 of these patients had incidental thyroid abnormalities, including 25 who had multiple small cysts (<4 mm).[1] The clinical and biochemical thyroid status of these patients was not reported. This study suggests that multiple, small, scattered thyroid cysts may be a common, incidental and asymptomatic finding in the pediatric thyroid.

In contrast, Kubota et al. in Japan reported that six middle-aged and elderly adult patients with small scattered thyroid cysts on ultrasound had thyroid auto-antibody negative hypothyroidism.[2,3] Kubota et al. termed the condition "polycystic thyroid disease."[2,3] In a further follow-up study of Japanese patients with antibody-negative hypothyroidism, polycystic thyroid (PCT) on ultrasound was associated with 7.8% of cases with overt hypothyroidism and 7.7% of cases of subclinical hypothyroidism.[1] Thus multiple small cysts of the thyroid appears be a risk factor for hypothyroidism particularly in adults.

More recently Naranjo et al. reported two Spanish children who were found to have thyroid antibody-negative, subclinical hypothyroidism incidentally discovered in the workup for short stature and monitoring of lithium therapy. These two patients both had PCT on ultrasound.[4] Thus, the clinical significance of PCT as a marker of hypothyroidism in children is unclear. In this report we wish to present and discuss eight pediatric patients with PCT along with their physical and laboratory findings, as well as the role of clinical follow up in this condition.

CLINICAL REPORT

Patient endocrine evaluation and thyroid ultrasonography was performed at the Children's Hospital of New Orleans, Louisiana. Ultrasounds were performed with a GE LOGIQ E9 device and used ML6/15 linear transducer. The volume of each lobe was calculated from the measurements of the depth (d), the width (w), and the length (l) of each lobe by the formula: Volume (ml) = 0.479 x d x w x l (cm)[5, 6]. The thyroid volume was the sum of the volumes of both lobes. The volume of the isthmus was not included. TSH and Free T4 were performed in the clinical laboratory of the Children's Hospital using an Immunochromatographic Membrane Assay (ICMA) and Electrochemiluminescence immunoassay (ECLIA), respectively. Anti-TPO (Antithyroperoxidase)and Anti-TG(Antithyroglobulin) antibodies were performed at Esoterix Endocrine using Chemiluminescense and ICMA, respectively. The intra-assay coefficient of variation was 4.2-5.19% for TSH and 3.29-5.01% for FT4. The inter-assay coefficient of variation was 7-12.7% for TSH and 4.7-5.8% for FT4. Patients treated with thyroxine received starting doses based on literature recommended (6-12 year- 4-5 mcg/kg ; > 12 year 2-3 mcg/kg) and titrated based on subsequent fT4 and TSH by their attending.

This study represents a retrospective deidentified case series review and does not require informed consent. It complied with standards of the LSUHSC Institutional review board for this type of clinical communication.

PATIENT DESCRIPTIONS

Summary of the initial presentation, thyroid hormone values and ultrasound findings for each patient are included in table 1.

Table 1

Patient	Age/Race	Sex	TSH (uIU/mL)	Free T4 (ng/dL)	Ultrasound Characteristics
#1	13 years White	Male	3.04 (0.36-3.74)	1.35 (0.79-1.5)	Multiple cysts throughout both thyroid lobes, most of them arranged at the periphery of the gland. Cysts range from 1-4 mm with two larger cysts measuring 4-5 mm in each thyroid lobe. Thyroid volume =9.3- 10.1 ml
#2	14 years White	Male	5.97 (0.3-4)	None *T4: 7.9 ug/dL (5.6-11.7)	Multiple cysts located at the periphery of both lobes. The largest cysts were located in the posterior inferior aspect of the left lobe of the thyroid and measured 6 mm and the posterior-inferior aspect of the right thyroid lobe measuring 5 mm. Thyroid volume = 12.4-13.5 ml .The larger cysts have focal punctate echogenicity in their center.
#3	14 years, 2 months African American	Female	2.45 (0.5-4.8)	0.9 (0.7-1.8)	Multiple cysts, mostly affecting the upper and midpole of the left thyroid lobe. Lesions measured between 3 and 5 mm. Thyroid volume =7.8-8.5 ml .Some cysts have focal punctate echogenicity.
#4	14 years, 5 months White	Male	3 (0.4-5)	1.1 (0.79-1.50)	Multiple cysts bilaterally, the largest measuring 5 mm in the right lobe. Some of them are arranged in a nodular pattern with interspaced solid tissue. Thyroid volume = 7.1-7.7 ml .Some cysts have focal punctate echogenicity.
#5	12 years White	Male	1.49 (0.36-3.74)	0.84 (0.79-1.5)	Multiple cysts bilaterally. The largest lesion measured 2.6 mm on the left lower pole of left thyroid lobe. Thyroid volume = 9.8-10.6 ml
#6	7 years, 10 months Hispanic	Female	3.70 (0.36-3.74)	1.14 (0.79-1.5)	Multiple small cysts bilaterally measuring 5-8 mm.
#7	14 years White	Female	2.97 (0.45-4.5)	1.06 (0.93-1.6)	Multiple small cysts bilaterally, <2 mm, mainly at the periphery of the gland.
#8	16 years, 5 months White	Female	0.96 (0.5-4.5)	1.26 (0.78-1.5)	Multiple small cysts bilaterally, mainly at the periphery of the gland. Thyroid volume = 8.3-9 ml

Table 1. Patient descriptions, thyroid function values and thyroid ultrasound characteristics. Anti-thyroglobulin and anti-thyroid peroxidase antibodies were negative in all patients. *T4 = Total Thyroxine

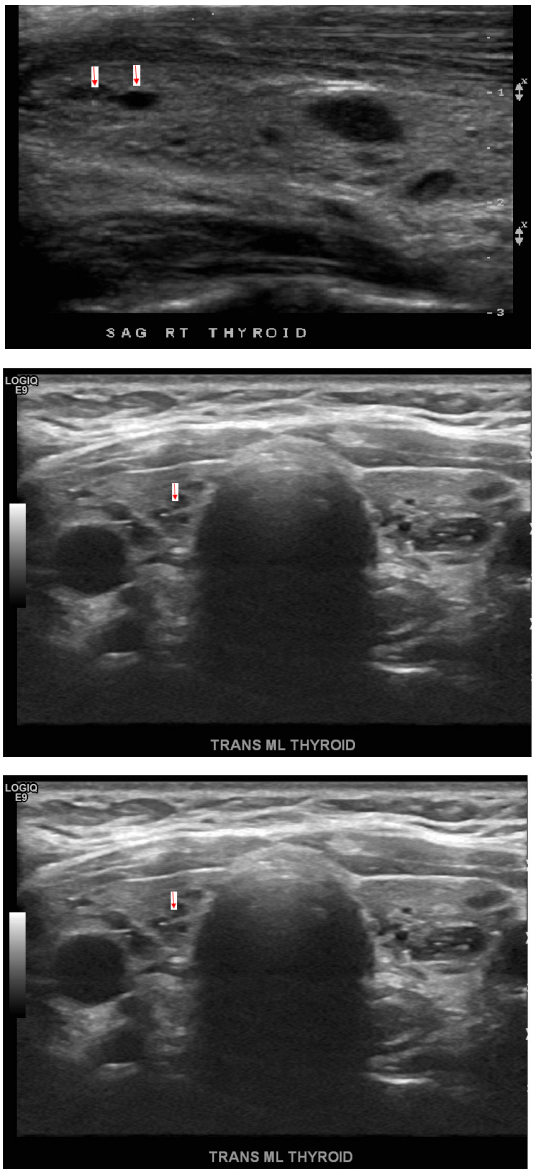

Figure. Thyroid ultrasound in patients 1 (top), 2 (middle), and 3 (bottom) are representative of the ultrasounds in all patients.

PATIENT 1

Patient was a 13 year old male who presented to the emergency department with complaints of fever and neck stiffness. Patient had been otherwise healthy and without symptoms or family history of thyroid disease. On exam, the patient had left tonsillar enlargement with left sided cervical lymphadenopathy, and no palpable goiter or thyroid nodules. On computerized tomographic (CT) imaging of the neck done for suspicion of retropharyngeal abscess, discovered a prominent thyroid with multiple cysts bilaterally. This patient was lost to follow up after the initial evaluation. Ultrasound findings are shown at the top of the Figure.

PATIENT 2

Patient was a 14 year old male referred to Endocrinology for evaluation of elevated TSH: 5.97 uIU/mL (0.3-4), normal total T4:7.9 ug/dL (5.6-11.7), and suspected thyroid nodule discovered during work up for obesity. He had no family history or symptoms of thyroid disease. US did not reveal a nodule, but scattered small multiple cysts were found. This patient was lost to follow up after the initial evaluation. Ultrasound findings are presented in the middle of the Figure.

PATIENT 3

Patient was a 14 year 2 month old female with Gorlin-Goltz syndrome (nevoid basal cell carcinoma syndrome) confirmed genetically after occurrence of ovarian tumors and multiple skin nevi. PCT was identified upon ultrasound imaging of the neck for evaluation of a left post-auricular lymph node and a small skin mole in the same area. The patient had a family history significant for Graves disease in two of her maternal aunts. Patient had no symptoms of thyroid disease. On physical exam no goiter or thyroid nodules were identified. Due to her mild thyroid enlargement and multiple cysts on ultrasound, she was started on levothyroxine therapy. Subsequent imaging over three years of follow up has shown no change in thyroid or cyst sizes. She continues to have negative thyroid specific antibodies. Ultrasound findings are presented at the bottom of the Figure.

PATIENT 4

Patient was a 14 year 5 month old male referred to endocrinology for evaluation of multiple thyroid cysts incidentally found during CT imaging of the neck after an automobile accident. He was otherwise healthy and without thyroid symptoms. Mother and maternal grandmother have a history of hypothyroidism of unclear etiology. Physical exam was normal. Over 24 months this patient has not had change in thyroid status.

PATIENT 5

Patient was a 12 year old male referred to Endocrinology for evaluation of a goiter. Patient denied symptoms of thyroid disease except weight gain of 12 pounds in the prior year. His past medical history is significant for cyclic neutropenia. Physical exam was significant for weight >95th percentile, and barely palpable thyroid gland with normal consistency and no nodules. Patient was started on levothyroxine therapy due to enlarged thyroid. After two years of follow-up, serial ultrasounds have not shown any change in thyroid or cyst size. He continues to be chemically euthyroid and repeat thyroid antibodies continue to be negative.

PATIENT 6

Patient was a 7 year 10 month old female referred to

Endocrinology for evaluation of a goiter. She was otherwise well and without symptoms of thyroid disease. Physical examination was significant for a body mass index (BMI) >97th percentile, she had prominent nuchal fat, and no distinct goiter or thyroid nodules.

PATIENT 7

Patient was a 14 year old female referred to Endocrinology for repeated stress fractures of foot. She was without symptoms of thyroid disease. Mother has Hashimoto's thyroiditis. Physical examination was significant for a BMI >97th percentile and a small, soft palpable goiter. This patient was recently evaluated and has not had follow-up for more than a few months.

PATIENT 8

Patient is a 16 year and 5 month old female referred for evaluation of goiter discovered incidentally during a routine annual visit. She had no symptoms of thyroid dysfunction and no family history of thyroid disease. Thyroid functions were normal, antithyroglobulin and antimicrosomal antibodies were negative.

DISCUSSION

We report clinical findings from eight pediatric patients (7-16 years of age) who had multiple small cysts scattered throughout an enlarged thyroid gland. This is the largest series of pediatric cases correlating ultrasound, clinical, biochemical findings, and preliminary follow up. In general most of the scans from our patients were characterized by slight thyroid gland enlargement with multiple scattered (but most often at the periphery) thyroid cysts without evidence of vascular changes or echogenicity. The cysts were of small size, < 6mm. Thyroid auto-antibodies were negative in all patients. Our pediatric patients were referred for endocrine evaluation after having been incidentally discovered to have a goiter or incidentally found to have a thyroid abnormality by imaging for a non-thyroid indication.

These ultrasound changes in our pediatric patients were similar to those previously described in a series of Japanese adults, and termed "polycystic thyroid disease" by Kubota et al.2,3,7 The Japanese patients were of much older age (60-81 years) and PCT was associated with 7.8% of cases with overt and 7.7% of cases of subclinical antibody-negative hypothyroidism.[1] Many adult patients with PCT who were initially euthyroid, eventually developed hypothyroidism.[2] Kubota et al. suspected that hypothyroidism in these patients developed secondary to cyst impingement on functional thyroid tissue combined with high dietary iodine intake, causing an impaired Wolff–Chaikoff effect.[2,7] In a small number of the Japanese patients with a high dietary intake of iodine, it was found that dietary iodine restriction in the hypothyroid patients led to a return to the euthyroid state.[7] The authors speculated that the presence of multiple cysts was a factor in the development of hypothyroidism, as iodine excess does not typically lead to hypothyroidism in healthy individuals without pre-existing thyroid disease.[8]

Kubota et al. obtained histopathological samples from their patients with PCT disease and compared them to patients with multinodular goiter.[3] PCT disease was characterized by enlarged colloid containing follicles of variable sizes, usually up to 5 mm.[3] The large follicles corresponded to the cysts that were detected by ultrasonography. The follicles were cuboidal and normal appearing. There were no findings of an aggregation of small follicles, papillary projection or degenerative changes in the follicles as would be found in multinodular goiters. Thus adult PCT disease has distinct ultrasound and histopathologic characteristics. When comparing ultrasound findings, multinodular goiters are often described as being heterogeneous, without well defined nodules or multiple nodules interspersed throughout a normal appearing gland.[9] Areas of hemorrhage, necrosis, and calcifications were often seen. In contrast, auto-immune thyroiditis presents with marked glandular hypoechogenicity, usually non-homogenous, as well as changes in vascularity on Doppler flow.[10, 11]

In a separate small case series of Japanese adults, the ultrasound finding of a localized area of multiple small cysts within the thyroid coalescing to give a honeycomb appearance was associated with papillary thyroid carcinoma.[12] This is in contrast to the presentation of PCT where cysts are scattered throughout the gland rather than localized to a discrete area.

Unlike the Japanese adult literature, PCT has not been classified as a distinct condition in children. However, in a survey of imaging studies of the neck performed for non-thyroid indications in Canada, Avula et al. reported incidental thyroid abnormalities in 52 scans of 287 ultrasounds where the entire thyroid was visible. Multiple scattered small thyroid cysts, similar to what was termed PCT by Kubota et al. accounted for 48% or 25 of the 52 abnormal thyroids.[1] Thus occurrence of pediatric PCT might be as high 8.7% (25 out of 287 scans). Avula did not comment on the clinical or laboratory status of the patients with abnormal thyroids. Thus the clinical significance of PCT from this report was left unclear.

More recently, two children with ultrasound findings of PCT were reported from Spain.[4] These patients were initially identified with antibody-negative, "subclinical hypothyroidism " (fT4 and TSH not reported in the article) in the course of evaluation for short stature in one, and for surveillance of lithium therapy for bipolar disorder in the other. Neither of these patients had goiters. Assuming these patients both had normal fT4 with increased TSH may indicate an initial deterioration in thyroid function, which is similar to the initial findings in patient 2 who presented with a slight elevation of TSH with normal total thyroxine levels. Unfortunately the clinical course of patient 2 is unknown as he was lost to follow up. Our other patients did not have initial abnormalities of free T4 or TSH or exhibit ultrasound or biochemical progression of disease.

One of our patients was known to have Gorlin-Goltz syndrome (patient 3), also known as nevoid basal cell carcinoma syndrome (NBCCS). NBCCS represents a series of multi-organ abnormalities known to be the consequence of abnormalities in the PTCH gene.13 These include basal cell carcinomas, skeletal abnormalities, facial dysmorphism, odontogenic keratocysts, medulloblastoma, ovarian fibromas, and less frequently, increased risk of all malignancies, including thyroid carcinoma.[14] This patient, was referred for endocrine evaluation incidental to the finding of multiple small thyroid cysts discovered on a neck imaging study for a non-thyroid indication. She has been followed on levothyroxine therapy for three years without changes in thyroid gland size or cysts. Benign thyroid cystic changes in NBCCS patients is not a previously reported part of the syndrome. As PCT may be a more commonly encountered incidental finding than previously appreciated the multiple small thyroid cysts discovered in our patient may not be part of the NBCCS syndrome.

There are several limitations of this case study. As the patients were otherwise healthy and there was no clinical progression, thyroid biopsies were not performed as had been previously done in the reports of Kubota et al.[3] In Japanese adult patients with PCT, hypothyroidism was associated with high dietary iodine intake. We did not assess iodine intake in our patients. However, dietary iodine content among children in the U.S. is generally not excessive[15] and potentially prevents deterioration to hypothyroidism. The period of follow up in our patient cohort was relatively brief. As most patients reported with overt hypothyroidism were adults, PCT may require a long period of time before hypothyroidism occurs and/or high dietary iodine. Many of the patients in our series were prophylactically started on thyroid replacement which may have prevented progression of pathology during follow-up.

In conclusion, we speculate that PCT has not been previously described as a distinct entity in pediatrics due to infrequent occurrence, subtlety of the clinical thyroid enlargement, and absence of overt clinical and biochemical hypothyroidism. Although pediatric PCT may be infrequent, non-progressive, and benign there has been no follow up of this entity from childhood into adulthood. Until there is further information on the long-term natural history of PCT discovered in the pediatric patients, we recommend periodic long-term follow up through adulthood.

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