RESEARCH ARTICLE

Low Value of Thyroid Testing in the Pediatric Inpatient Setting

Ahmed Torky, MD,[a] Meredith LaRue, CFNP,[b] Paul Kaplowitz, MD, PhD[b]

ABSTRACT

OBJECTIVES: Our objective was to assess the frequency of pediatric inpatient thyroid testing, frequency of detection of abnormal results, and apparent impact on patient management.

METHODS: This is a retrospective study of admissions from July 2015 to June 2016 at a large urban children's hospital. Chart review was conducted on all hospitalized pediatric patients who underwent thyroid testing. We used a normal range of 0.5 to 5.0 μIU/mL for thyroid-stimulating hormone (TSH) and 1.0 to 2.0 ng/dL for free thyroxine (FT4), except for neonates for whom we used the higher reference ranges specified by the hospital laboratory.

RESULTS: Thyroid testing occurred in 1202 (5.7%) of 20 907 hospitalizations; 79.3% had combined thyroid function tests (TFTs) with TSH + FT4 being most common, and 20.6% had TSH only. Combined TFTs were ordered routinely by psychiatry and frequently by endocrine, gastrointestinal, cardiology, and neurology services, but many cases had no identified reason for testing. Of the 205 abnormal tests (17.1%), the most common abnormalities in the combined TFTs group were normal FT4 and increased TSH (35.4%) (76% of which were between 5 and 10 μIU/mL), normal FT4 and TSH 0.1 to 0.5 μIU/mL (33.1%), and high FT4 but normal TSH (14.3%). Patients with new-onset type 1 diabetes had borderline low or high TSH in about 20% of cases, but all abnormalities resolved at outpatient follow-up. Overall, 8 patients (0.66%) were started on levothyroxine.

CONCLUSIONS: Pediatric inpatient thyroid testing is relatively common at our institution, and although results are often abnormal, they do not point to thyroid disease that has contributed to the reason for hospitalization and do not identify patients in urgent need of starting therapy.

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Address correspondence to Paul Kaplowitz, MD, PhD. E-mail: pkaplowi@childrensnational.org

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Dr Torky designed the system for characterizing the test results, did many of the chart reviews, wrote the first draft of the manuscript, and designed the tables; Ms Larue helped design the system for characterizing the test results and did many of the chart reviews; Dr Kaplowitz conceptualized the study, did some of the chart reviews, and did extensive work revising the manuscript; and all authors approved the final manuscript as submitted.

[a]*Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland; and* [b]*Division of Endocrinology, Children's National Health System and School of Medicine and Health Sciences, George Washington University, Washington, DC*

In the outpatient setting, because of reliable assays and easy availability, thyroid function tests (TFTs) are widely conducted when hypothyroidism or hyperthyroidism is suspected. When testing is done for indications such as long-standing obesity or family history of thyroid disease, it frequently gives borderline abnormal results, especially thyrotropin (TSH) levels in the slightly elevated (5–10 μIU/mL) range associated with a normal free thyroxine (FT4) level.

In the inpatient setting, recommendations on when and whom to test for a thyroid problem are scarce. The adult medicine literature reveals some contradictory results; 1 study revealed a high incidence of undiagnosed thyroid disease picked up by universal screening of all admitted patients, with only 3% of those patients picked up by screening having had thyroid testing done before admission.[1] Authors of other studies make the argument that nonthyroid illness (often referred to as sick euthyroid syndrome) and some medications can affect the results of thyroid testing, and in the lack of strong clinical suspicion of thyroid disease, there is no urgency to diagnose thyroid diseases in hospitalized patients.[2]

Specific inpatient conditions for which routine thyroid testing often occurs include patients with new-onset type 1 diabetes who are screened because of an increased risk of autoimmune hypothyroidism (the American Diabetes Association recommends TSH screening at diagnosis when the patient is clinically stable or after control has been established[3]), psychiatric hospitalizations, and the use of certain medications such as amiodarone and heparin. Heparin can affect FT4 testing only without clinical effect, whereas amiodarone can have a wide range of effects on the thyroid gland.

Our aim with this study was to assess how frequently tests ordered in the inpatient setting over the course of 1 year fell outside the normal range and how often they contributed to ongoing medical care.

METHODS

This study was approved by our institutional review board. It was a retrospective chart review of all patients hospitalized at Children's National Medical Center between July 1, 2015, and June 30, 2016, who had either TSH alone or TSH with any combination of FT4, free triiodothyronine (FT3), total thyroxine (T4), or total triiodothyronine (T3).

The method used for FT4 and FT3 in our hospital is equilibrium dialysis combined with tandem mass spectrometry. Normal ranges used for the neonatal period were the reference ranges provided by the laboratory, because higher levels of TSH and FT4 are expected; after the neonatal period, we used fixed values that differed slightly from laboratory reference values but were felt to reflect consensus normal values by endocrinologists (FT4: 1.0 to 2.0 [ng/dL] and TSH: 0.5 to 5.0 [mIU/mL]).

In an attempt to objectively analyze clinical reasoning, chart notes were reviewed for the days around the timing of thyroid testing and checked for the service ordering the test, clinical indications for ordering them, and medications possibly affecting results. In the many instances when a reason was not documented, the patient problem list was used to identify possible reasons for testing. Charts were also reviewed to assess the interpretation of the tests and whether it affected ongoing care and/or resulted in starting treatment or change in medication dose for thyroid disease. We noted if the endocrinology service wrote a consult note, but for many patients with mildly abnormal tests, it was common for our service to verbally reassure the providers that no further testing or treatment was needed. Finally, patients with the most abnormal test results were followed-up in the medical record as of December 31, 2016, to see if abnormal tests had been repeated and if the patients were on treatment for hypo- or hyperthyroidism.

We divided the patients in 2 main categories (those who had TSH only and those who had TSH plus at least 1 other test). If TSH was done first and because of an abnormal result, FT4 was added, which was the case in only 12 patients; those patients were considered as part of the combined TFTs group.

Patients with TSH only were further subdivided into normal (0.5–5.0), low TSH (<0.5), and high TSH (>5.0). Patients in the combined TFT group were subdivided into groups on the basis of whether the FT4 was low, normal, or high, and the TSH was either suppressed (<0.1), low (0.1–0.49), normal, or high. The reason for having a separate category for TSH <0.1 is that levels that low raise concern for possible hyperthyroidism, which is rarely found in patients with TSH ranging from 0.1 to 0.49.

RESULTS

Out of 20 907 patients admitted between July 2015 and June 2016, 1202 (5.7%) patients had thyroid testing done. The majority of those patients had combined TFTs (79.3%), with the most common combination being TSH and FT4 (see Table 1). We identified 404 patients who had an FT3 done, and nearly all (96.5%) were from the psychiatry service, which routinely ordered FT4, FT3, and TSH as part of their standard inpatient admission orders.

Reasons for Testing

Many patients in the TSH-only group were from the endocrine service (33.1%), because it is our practice to order TSH without FT4 on all patients with newly diagnosed type 1 diabetes.

Reasons for ordering TFTs are summarized in Table 2; it was notable that 41.6% of testing was done by the psychiatry service. We could not find any documented or inferred reason for testing in 12.8% of patients' charts.

In the remaining cases, endocrine causes represented the highest percentage, with

TABLE 1 Types of Thyroid Testing Ordered

Test	No. Patients (%)
Any thyroid testing	1202
TSH only	248 (20.6)
TSH + other thyroid tests	954 (79.3)
Other thyroid tests	950
T4	66 (6.9)
FT4	915 (96.3)
T3	10 (1.1)
FT3	404 (42.6)

TABLE 2 TFTs by Reason and Service Ordering the Test (TSH Only and Combined TFTs)

Specialty	No. Patients (%)
Psychiatry	501 (41.6)
Unknown reason	154 (12.8)
Endocrine	179 (14.9)
New-onset diabetes	104 (58.1)
Pituitary assessment	23 (12.8)
Preexisting thyroid disease	28 (15.6)
Hypoglycemia	11 (6.1)
Other	13 (7.3)
Gastrointestinal	88 (7.3)
Constipation	39 (44.3)
FTT	36 (40.1)
Anorexia	4 (4.5)
Other	9 (10.2)
Neurology	77 (6.4)
Seizures	31 (40.2)
Ataxia	7 (9.1)
Behavioral changes	5 (6.5)
Developmental delays	4 (5.2)
Other	30 (39.0)
Cardiology	52 (4.4)
Amiodarone use	22 (42.3)
Tachycardia	12 (23.1)
Arrhythmia (not on amiodarone)	7 (13.4)
Bradycardia	4 (7.7)
Other	7 (13.5)
Orthopedics	17 (1.4)
Fracture	10 (58.8)
Slipped capital femoral epiphysis	7 (41.2)
Hematology or oncology	13 (1.1)
Low bone mineral density	3 (23.1)
BMT	3 (23.1)
Goiter	2 (15.3)
Other	5 (38.5)
NICU (not including NBS) or PICU	23 (1.9)
Jaundice	7 (30.4)
Hypothermia	3 (13)
Maternal hypothyroidism	1 (4.3)
Other	12 (52.1)
Miscellaneous	98 (8.2)
Abnormal newborn screening	34 (34.7)
Trisomy 21	21 (21.4)
Obesity	14 (14.3)
Lithium use	6 (6.1)
Dysfunctional uterine bleed	6 (6.1)
Previous evidence of abnormal thyroid function	2 (2.0)
Other specialties	15 (15.3)

BMT, blood marrow transplant; FTT, failure to thrive; NBS, newborn screening.

14.9% of testing, of which 58.1% were done for patients with new-onset diabetes. Gastrointestinal causes represented 7.3% of testing, with constipation and failure to thrive being the most common. Neurologic causes represented 6.4% of testing, with seizures representing the most common reason, but a wide variety of other symptoms resulted in ordering TFTs as well.

Categories of Abnormal Tests

A total of 205 patients had abnormal tests representing 17.1% of all patients tested.

TSH Only

For patients with TSH only tested, 30 of 248 (12.1%) had an abnormal TSH, which was low in 16 patients ranging between 0.15 and 0.49 μIU/mL. Of those 16 patients with low TSH, 8 were patients with newly diagnosed type 1 diabetes.

Of the 14 patients with elevated TSH (13 with TSH 5.0–10.7 and 1 patient with TSH 26.4), 6 were newly diagnosed patients with diabetes, most of whom presented in diabetic ketoacidosis (DKA). Of note, none of the patients with slightly high TSH were treated, and their TSH normalized on subsequent outpatient testing.

Combined TFTs

Patients with combined TFT abnormalities (Table 3) revealed a high proportion of normal FT4 and high TSH (35.4%, of which 76% were in the 5–10 μIU/mL range, which we have defined as "slightly elevated"), normal FT4 and low but not completely suppressed (ie, >0.1 μIU/mL) TSH (33.1%), and elevated FT4 but normal TSH (14.3%). Few patients were identified with low FT4 and high TSH (0.6%) or low FT4 and low or normal TSH (1.7%), results that may indicate the need for treatment.

Specific Conditions

Type 1 Diabetes Mellitus

Analysis of patients with new-onset type 1 diabetes, in whom testing was almost always done in the first 24 hours of admission, shows that new-onset patients presenting in DKA ($n = 52$) had abnormal TSH in 21.1% of cases, whereas new-onset patients not in DKA ($n = 52$) had abnormal TSH in 17.3% of cases (difference not significant).

For patients presenting in DKA with abnormal TSH, 72.7% had low TSH, whereas patients not in DKA with an abnormal TSH had a near-equal likelihood of elevated versus suppressed TSH (44.4% and 55.6%, respectively).

None of the patients with diabetes with abnormal TSH were started on treatment during or right after their hospital stay. All those with abnormal TSH had it repeated, usually at their first follow-up visit, and all normalized; thus, none were on treatment as of the last chart review.

Amiodarone

We identified 22 patients taking amiodarone who had TFTs; 9 had normal TFTs, 7 had elevated TSH, 2 had high FT4 (one of which had low TSH), and 4 had both high FT4 and TSH. Only 1 (FT4 2.32 and TSH 68.9) was treated briefly with levothyroxine (L-T4) by the cardiac intensive care service.

Trisomy 21

Eleven patients with trisomy 21 were tested with combined TFTs, most of whom ($n = 9$) showed abnormalities primarily with high TSH and a normal FT4 ($n = 7$), with the 2 remaining patients showing an elevation in both the TSH and the FT4.

Preexisting Thyroid Disease

Patients with hypothyroidism already on replacement therapy were also noted in our cohort ($n = 25$), and a high percentage of abnormalities were noted ($n = 11$; 44%). They varied widely, with 4 patients showing high TSH and normal FT4, 2 patients showing low TSH and normal FT4, and the remainder distributed among other possibilities. Testing resulted in only 3 patients having dose alterations.

TABLE 3 Types of Abnormal Combined TFTs Found (n = 175; 14.6% of All Patients Tested)

Categories of Abnormal Test Results; TSH + FT4 (No T4 or T3 Reported)	% of Abnormal Combined TFT Results
Low FT4 or low T4 + normal or low TSH	1.7
Normal FT4 + low TSH (0.1–0.5)	33.1
Normal FT4 + suppressed TSH (<0.1)	6.9
Low FT4 + high TSH	0.6
Normal FT4 + high TSH	35.4
High FT4 + normal TSH	14.3
High FT4 + low TSH (0.1–0.5)	1.1
High FT4 + low TSH (<0.1)	2.3
High FT4 + high TSH	4.6

Repeat Testing

During the studied time period, we identified 38 patients who underwent 67 repeat thyroid tests.

Most repeat tests were obtained for mild abnormalities in TSH, and 58.8% of repeat tests were normal. Abnormal repeat tests were seen most commonly in patients exposed to amiodarone (23.5% of abnormal) and patients on thyroxine therapy (14.8% of abnormal).

With Table 4, we provide specific clinical details on the patients with the most concerning thyroid tests. Several tests were abnormal enough that treatment with L-T4 was started, although in some of those cases, the abnormality may have resolved on its own. For example, patients 3, 6, and 7 were euthyroid at 18 months to 2 years of age on a small dose of 25-μg L-T4, suggesting that their elevated TSH may have been transient in nature. The authors did not identify any cases in which an abnormal test result was clearly linked to the cause of hospitalization or other described morbidities. Patient 10 on the psychiatry service had tests consistent with hyperthyroidism, which conceivably could have contributed to her overdose, but review of her medical record revealed no documented preexisting signs or symptoms of thyroid hormone excess, and she was lost to follow-up before the endocrinology service could be consulted.

Overall, 8 patients (0.66%) with thyroid test abnormalities were started on medications, 3 of whom had trisomy 21, 2 with abnormal newborn metabolic screening, 1 patient in the oncology service who had a goiter noted on admission examination, a neonate exposed to amiodarone with normal FT4 and high TSH, and 1 patient who was admitted to the hospital for thyroidectomy.

DISCUSSION

This study was undertaken to determine the frequency of inpatient thyroid testing in a large pediatric hospital over the course of 1 year, the frequency of abnormal results, and the apparent impact of testing on subsequent care. There are few previous studies of these questions in the literature and none in which authors focus on testing in children without psychiatric disorders.

In a systematic review of literature for the years between 1966 and 1999 that was used to examine TFTs in the adult inpatient population, researchers found that the prevalence of thyroid diseases in those studies was similar to the prevalence reported in outpatient studies and that the absence of thyroid symptoms lowered the pretest probability and made screening less useful.[4]

To our knowledge, data used to examine thyroid testing in the pediatric inpatient population are limited to 1 study in which authors looked specifically at the adolescent psychiatric population, in which 196 patients underwent thyroid testing, none of whom had clinical evidence of thyroid disease. Testing identified 10 patients with abnormal TFTs, 5 of whom were tested later and showed normal TFTs, and none were started on thyroid medication.[5] Although thyroid disease has been linked to a wide range of diseases from psychosis to mood disorders, guidelines for screening psychiatric patients for thyroid diseases are limited, and authors of most well-structured studies recommend against universal screening unless there is a strong clinical suspicion.[6,7] As a result of our study, the psychiatry service at our hospital is now ordering thyroid tests only when there is clinical suspicion of a thyroid problem.

Nonthyroid illness syndrome is a well described phenomenon in which sick patients have decreased T4 and/or T3 levels without elevation of TSH or evidence of any abnormality in the pituitary–thyroid axis. Several pathophysiological pathways have been proposed.[8] Curiously, we identified a combination of low FT4 and nonelevated TSH in only 1.5% of our abnormal tests, whereas we far more often found normal FT4 and low TSH (33% of our abnormal tests); this may suggest that in sick children, TSH may be more often affected than FT4. Another possibility is that our method for FT4, which is equilibrium dialysis–tandem mass spectrometry, has been found to be less affected by the metabolic changes of acute illness, including low-binding proteins, than older immunoassay methods for measuring FT4.[9]

Another potential cause of low FT4 with nonelevated TSH is hypopituitarism, and thyroid testing is appropriate when there is clinical suspicion of that diagnosis, such as detection of an ectopic posterior pituitary on MRI. Although testing for possible hypopituitarism was done in 29 children, no cases of low FT4 due to a new diagnosis of hypopituitarism were identified.

Patients with DKA can be in a state of stress severe enough to affect thyroid functions, and we did find either low or elevated TSH in 21% of such patients, which normalized after follow-up. Authors of other studies have reported on the low benefit of thyroid testing in patients with DKA[10,11]; similar to our cohort, patients with abnormal tests on admission normalize when repeated later. This makes the usefulness of screening for thyroid disease in inpatients presenting with new-onset type 1 diabetes, especially those presenting in DKA, questionable, and

TABLE 4 Clinical Details on Patients With the Most Abnormal Thyroid Test Results

Patient No.	Age	Reason for Test	TSH, mIU/mL	FT4, ng/dL	Relevant Medications	Consequences	Long-term Follow-up
1	3.5 wk	Amiodarone therapy due to arrhythmia in a premature infant with complex cardiac disease	68.9	2.32	Amiodarone	Endocrine not consulted; started on L-T4	Treated for 2 wk, then L-T4 was stopped; 9 d later, FT4 was 1.58, and TSH was 13. No further testing was done.
2	5 mo	Patient with trisomy 21 was admitted for repair of septal defect. The patient had tachyarrhythmia in the postoperation period.	17.9	1.8	None	Endocrine was not consulted	None
3	5 y	Cardiac patient who had surgery in an outside facility. TFTs were done before transfer (unclear why) and TSH elevated.	17.5	1.6	None	Endocrine consulted and managing him since	1 y later, TSH was 8.2, and FT4 was 1.8; no therapy was started.
4	1 wk	Patient with trisomy 21 with congenital heart disease. TFTs were done in outside hospital (unclear why); TSH 14 with FT4 2.08.	14.04	1.5	None	Started on thyroid replacement with L-T4	At the age of 2 y, patient euthyroid on L-T4 25 μg.
5	7 mo	Failure to thrive	12.37	1.47	None	Endocrine consulted	Followed-up and TSH had normalized
6	90 d	BW 888 g infant transferred for large PDA; newborn thyroid screening was said to be normal at referring hospital.	155	1.34	None	Started on thyroid replacement with L-T4	At age of 2 y, patient euthyroid on L-T4 25 μg
7	3 wk	Trisomy 21	32.2	3.14	Heparin	Started on thyroid replacement with L-T4	At the age of 18 mo, patient euthyroid on L-T4 25 μg.
8	8 y	Goiter was discovered during admission to hematology-oncology service	141	0.9	None	Started on thyroid replacement with L-T4	Continues to be treated with L-T4
9	14 y	Hypertension	0.29	2.5	None	Endocrine not consulted	5 mo later at follow-up visit, TFTs had normalized
10	15 y	Admitted to psychiatry service for acetaminophen ingestion; pulse: 60–80. Neck examination was documented in chart as normal.	0.09	5.7	None	Psychiatry service missed result; endocrine not consulted	Lost to follow-up
11	3 wk	2-wk-old ex 39 wk with complex cardiac condition	26.4	Not done	None	Patient died 2 wk later because of cardiac complications	N/A

BW, birth weight; N/A, not applicable; PDA, patent ductus arteriosus.

our findings support the American Diabetes Association guidelines, which suggest deferring TSH testing until the patient has clinically stabilized.[3]

Thyroid testing was common in patients in the ICU, particularly those in the cardiac and neonatal ICUs often as a follow-up to abnormal newborn screening in the NICU or to assist in the workup of arrhythmias in the cardiac ICU. However, thyroid abnormalities rarely contribute to arrhythmias in the early months of life, except perhaps when the mother and infant have hyperthyroidism. Amiodarone therapy is also one of the common reasons for testing, but guidelines on how to manage those patients in the pediatric age range is lacking. Amiodarone, which has a high iodine content, can affect the gland by several mechanisms, including type 1 and type 2 amiodarone-induced hyperthyroidism.[12] Despite a high number of abnormal test results, none of the 17 patients on amiodarone therapy had either clear hyperthyroidism or both a low FT4 and an elevated TSH, although 1 patient with a high FT4 and very high TSH was briefly treated. Because many such patients are neonates with critical congenital heart disease, one must balance the known importance of thyroid hormone for the developing brain and the critical status of their heart disease, which calls for extra caution before starting thyroid replacement.

Patients with trisomy 21 are at increased risk for both hypothyroidism and hyperthyroidism. The prevalence of thyroid disease in different studies ranges from 8% to 49% depending in part on how thyroid disease is defined, but a large proportion of those patients have normal FT4 with mildly

elevated TSH,[13] as we found in our inpatient sample. The American Academy of Pediatrics recommends checking TSH at 6 months, 1 year, and then annually thereafter.[14] Mild elevation of TSH in trisomy 21, even those cases with positive antibodies or those with presumed congenital hypothyroidism, can normalize later. Thus, some recommend retesting in 2 to 3 months rather than starting therapy.[13] In addition, the usefulness of routine inpatient testing in children already taking L-T4 may be questioned, because these patients are in most cases having their TFTs monitored on a regular basis by their endocrine provider.

The cost of thyroid testing also needs to be considered when assessing the cost-effectiveness of testing in the inpatient setting. In our hospital, the amounts insurance is billed for these tests are as follows: FT4 ($252), FT3 ($326), T4 ($133), and TSH ($270). The total charges for these tests using only the first test ordered for each patient was close to $700 000 for 1 year. Excluding situations when testing was done to rule out endocrine causes such as hypopituitarism, one can argue, given that we rarely found low FT4 with normal TSH, that TSH alone can in most cases be used as the screening test for thyroid disease. This change would decrease the cost of testing significantly.

There are limitations of evaluating the use and value of testing using a retrospective chart review, in that the indications for testing and impact on management are not always clear. There may have been benefits from abnormal tests that were not discernible by chart review or benefits of normal results in some cases, including reassurance. Additionally, with this investigation, we did not assess under testing (ie, the absence of thyroid testing in those who may have benefited).

CONCLUSIONS

We have demonstrated that in the absence of strong clinical suspicion, thyroid testing done in the pediatric inpatient setting rarely contributes to a better understanding of the reason for hospitalization or in identifying patients in urgent need of starting or modifying treatment. Although abnormal results are common, they generally do not point to underlying thyroid illness and typically normalize without intervention.

Providing education to inpatient providers to reduce inpatient thyroid testing, such as the one undertaken with our inpatient psychiatry service, ordering TSH only in most cases, and delaying testing until outpatient follow-up in patients admitted for new-onset diabetes, could reduce unnecessary laboratory and consultation costs without negatively impacting patient care.

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