Published in final edited form as:
Clin Pediatr (Phila). 2012 February ; 51(2): 160–164. doi:10.1177/0009922811418823.

Detours on the Road to Diagnosis of Graves Disease

Emily K. Sims, MD[1], **Erica A. Eugster, MD**[1], and **Todd D. Nebesio, MD**[1]

[1]Riley Hospital for Children, Indianapolis, IN, USA

Abstract

Objectives—The aims of this study were to determine the frequency at which spurious diagnoses and unnecessary treatment occurs prior to the diagnosis of Graves disease (GD) and to evaluate the economic consequences of these events.

Methods—Retrospective chart review of children diagnosed with GD.

Results—A total of 76 children (61 girls) aged 11.9 ± 3.8 years were identified. In all, 17 (22.4%) were referred to other subspecialists prior to diagnosis of GD. Six were hospitalized, and 2 visited emergency rooms. A total of 15 (19.7%) underwent nonthyroid-related studies. Estimated cost of testing and procedures ranged from $49 to $14 000. Twelve (15.8%) were diagnosed with attention deficit/hyperactivity disorder, and 16 (21.1%) were started on medications for other conditions prior to diagnosis of GD.

Conclusions—Evaluation and treatment for presumed other disorders are common in children with GD. A high index of suspicion for hyperthyroidism by primary care providers may help to avoid clinical detours that may be costly and delay diagnosis.

Keywords

Graves disease; pediatrics; hyperthyroidism; diagnosis

Introduction

Graves disease (GD) is the most common cause of hyperthyroidism in pediatric patients.[1] Children may present with a wide variety of symptoms differing in severity from minor to life threatening and affecting a range of organ systems. Classic symptoms include heat intolerance, increased appetite, weight loss, eye changes, palpitations, insomnia, inattentiveness, and school and behavior problems. Characteristic physical findings include tachycardia, widened pulse pressure, goiter, fine tremor, and hyperreflexia.[1–8] However, the presence of a goiter may be missed on casual physical examination and the signs and

Corresponding Author: Emily K. Sims, Riley Hospital for Children, 705 Riley Hospital Drive, Room 5960, Indianapolis, IN 46202, USA, eksims@iupui.edu.

Declaration of Conflicting Interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

symptoms of hyperthyroidism share significant overlap with several other conditions. This, combined with an often insidious onset, can create a substantial barrier to diagnosis.[2–5]

Prior to being seen by a pediatric endocrinologist, children with hyperthyroidism may be referred to other subspecialists to be evaluated for other conditions. A delay in diagnosis not only prolongs the disease course, but it can also be dangerous if symptoms progress in severity.[2] Unnecessary testing and procedures pose risks and costs without providing benefit to the patient. How often this occurs in children ultimately diagnosed with GD has not been systematically investigated. Therefore, the objective of our study was to identify and characterize situations in which there was confusion and a delay in diagnosis because of the symptoms of hyperthyroidism being mistaken for other medical conditions in children with GD seen in our clinic over a 10-year period.

Patients and Methods

After institutional review board approval, a retrospective chart review of children with GD seen in the Pediatric Endocrinology Clinic at Riley Hospital for Children from 1998 to 2007 was performed. Subjects were identified by diagnostic ICD-9 (International classification of Diseases–9th revision) codes for hyperthyroidism and iatrogenic hypothyroidism, including 242.00, 242.01, 242.90, 242.91, 244.1, and 244.2.

All children were diagnosed with GD by a pediatric endocrinologist and had biochemical confirmation of hyperthyroidism, including decreased thyrotropin and elevated thyroxine and/or triiodothyronine levels. All patients had confirmation of GD with positive autoimmune antibody markers or an increased thyroid uptake scan. Data evaluated included gender, race, insurance status, age at diagnosis, pubertal stage, symptoms at presentation, duration of symptoms, previous testing and procedures, previous subspecialty evaluation, medications, and history of hospital encounters secondary to symptoms. Data were obtained from the medical records of the pediatric endocrinology clinic, some of which included records that had been sent by the primary care provider. Any patient in whom the clinical diagnosis was questioned, uptake scan or biochemical testing was inconsistent with GD, or medical records were incomplete, was excluded.

Estimated costs of tests and procedures were estimated using the 2009 facility, lab, and procedure fees for Riley Hospital for Children. For certain procedures that involved specialized techniques and a wide range of potential expense, the most conservative cost is reported. Cost estimates do not include the physicians' procedure or reading fee.

Statistical analyses were performed using Microsoft Excel to calculate means and standard deviations.

Results

A total of 76 subjects (61 girls) aged 11.9 ± 3.8 years (2.8–17.7 years) with GD were identified. The majority of the patients were Caucasian (75.0%), 14.5% were African American, and 3.9% were Hispanic. Most patients had private insurance (77.6%). Medicaid served as the primary insurance in 13.7%, and 7.9% were self-pay. Thirty-eight patients

(50.0%) were pubertal, 29 (38.2%) were prepubertal, and 9 (11.8%) did not have pubertal status documented at the time of diagnosis of GD.

Mean duration of symptoms in the 57 patients in whom it was documented was 9.6 ± 11.7 months with a range of 0.5 to 78 months. The number of reported symptoms ranged from 1 to 16 with a mean of 6.8 ± 3.1. Symptoms present in at least 10% of patients are listed in Table 1. Although only 35.5% of patients reported neck enlargement, 94.4% had thyromegaly documented on exam. No association was observed between specific symptoms and duration of delay in diagnosis of GD.

In total, 17 patients (22.4%) were referred to other subspecialists prior to the diagnosis of GD, and 5 (6.6%) were evaluated by more than one subspecialist. The most common referrals were to cardiology (21.4%), followed by psychiatry (17.9%), gastroenterology (14.3%), ophthalmology (10.7%), dermatology (7.1%), ear, nose, and throat (7.1%), neurology (7.1%), rheumatology (7.1%), and neurosurgery (3.6%). Before being diagnosed with GD, 15 patients (19.7%) underwent nonthyroid evaluation, including blood tests, imaging studies, and medical procedures. Organ systems investigated most frequently included cardiac (28.3%), gastrointestinal (23.9%), neurologic (21.7%), and genitourinary (6.5%). Procedures as well as their associated costs are summarized in Table 2. Six patients were hospitalized for disease related symptoms and 2 visited emergency rooms. Three of the inpatient stays involved the intensive care unit (ICU) for conditions eventually attributed to hyperthyroidism and thyroid storm. Patients who were admitted to the hospital with symptoms eventually found to be due to hyperthyroidism are further characterized in Table 3.

Prior to the diagnosis of GD, 12 patients (15.8%) were diagnosed with attention deficit/hyperactivity disorder (ADHD), and 16 children (21.1%) were started on various medications. The following categories of medications were initiated in more than one child: psychostimulants (15.8%), antidepressants (5.3%), antireflux agents (5.3%), antihypertensives (3.9%), and bronchodilators (2.6%).

Discussion

Isolated case reports have emphasized the potential for children with GD to come to medical attention in a myriad of ways.[9–17] A delay in diagnosis is particularly common in prepubertal children, who have a propensity to present with atypical symptoms.[18] However, the frequency of spurious diagnoses and subspecialty evaluation in children ultimately diagnosed with GD has not been established. Although the signs and symptoms of GD are well established, to our knowledge, our study is the first to systematically examine previous evaluations and diagnoses in a large cohort of pediatric patients with GD.[4,5] Nearly one fourth of our patients were referred to another subspecialist before being seen by a pediatric endocrinologist, and 13% were seen in the hospital on an emergent basis. Our finding that cardiology evaluations were the most frequently obtained subspecialty referral is consistent with reports that 23% of pediatric hyperthyroid patients present with a chief complaint that is cardiac in nature.[19] Although a few of our patients had extremely rare presentations, the vast majority had classic signs and symptoms of GD, including thyroid enlargement in 94%

of cases. Most patients were not part of an underserved population and so presumably had access to health care. Unfortunately, a delay in diagnosis resulted in increased severity of hyperthyroidism in several cases, which is dangerous and potentially life threatening. This underscores the importance of early recognition of symptoms in reducing morbidity in children with GD.

Interestingly, the prevalence of an ADHD diagnosis in our patients was twice that of the estimated prevalence in Indiana in 2003 (15.8% vs 7.93%).[20] Given the frequency of neurocognitive symptoms, such as inattentiveness in children with hyperthyroidism, it is tempting to speculate that the diagnosis of ADHD was erroneous. Ongoing follow-up will be necessary to determine whether or not this was the case.

In light of rising health care costs, minimizing unnecessary expenditures also presents a pertinent consideration. As noted in Table 2, many of the interventions obtained were costly. At our institution in 2009, an intermediate level emergency room visit not including labs, imaging, consultation, or procedures resulted in a patient charge of approximately $665. The average daily inpatient charge ranged from $1700 to $3300 depending on whether the patient occupied a ward or ICU bed. These large sums dwarf the cost of screening with a thyrotropin level ($170 at our institution in 2009) and highlight the economic benefit of careful choices in diagnostic decision making.

There are several limitations to our study. As it was retrospective, identification of cases and events antecedent to the diagnosis of GD depended on accurate documentation in the medical record. Another limitation is that many hyperthyroid symptoms are nonspecific, and it is possible that bona fide concurrent medical disorders may have been present in a subset of our patients with GD. This study only examined symptoms at presentation, and we did not determine if the symptoms resolved after initiation of therapy. However, no documentation existed in the medical record to suggest that the tests listed in Table 2 were performed to evaluate nonthyroid coexisting conditions. Finally, cost determination was based on established fees at our institution, and because available data for other hospitals is lacking, we are unable to comment on charges for similar procedures obtained elsewhere. Nonetheless, we approached estimates conservatively to avoid overemphasizing the costs of various procedures, omitting physician fees, and our estimates likely underrepresent overall expense.

Conclusions

Hindsight and retrospective review of cases provide a clear link between the presenting signs and symptoms and the eventual diagnosis of GD. A careful review of systems and physical examination combined with a low threshold for thyroid function testing on the part of primary care physicians may result in many hyperthyroid children being detected earlier. A high index of suspicion for GD may ultimately help to prevent unnecessary and expensive evaluation and treatment, as well as lead to a timely diagnosis and appropriate management.

Acknowledgments

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Rivkees SA, Sklar C, Freemark M. Clinical review 99: the management of Graves' disease in children, with special emphasis on radioiodine treatment. J Clin Endocrinol Metab. 1998; 83:3767–3776. [PubMed: 9814445]
2. Birrell G, Cheetham T. Juvenile thyrotoxicosis: can we do better? Arch Dis Child. 2004; 89:745–750. [PubMed: 15269076]
3. Bettendorf M. Thyroid disorders in children from birth to adolescence. Eur J Nucl Med Mol Imaging. 2002; 29(suppl 2):S439–S446. [PubMed: 12192543]
4. Lazar L, Kalter-Leibovici O, Pertzelan A, Weintrob N, Josefsberg Z, Phillip M. Thyrotoxicosis in prepubertal children compared with pubertal and postpubertal patients. J Clin Endocrinol Metab. 2000; 85:3678–3682. [PubMed: 11061522]
5. Shulman DI, Muhar I, Jorgensen EV, Diamond FB, Bercu BB, Root AW. Autoimmune hyperthyroidism in prepubertal children and adolescents: comparison of clinical and biochemical features at diagnosis and responses to medical therapy. Thyroid. 1997; 7:755–760. [PubMed: 9349579]
6. Eberle A. Hyperactivity and Graves' disease. J Am Acad Child Adolesc Psychiatry. 1995; 34:973–974. [PubMed: 7665452]
7. McCune N, Ritchie K. ADHD/thyroid dysfunction. J Am Acad Child Adolesc Psychiatry. 1997; 36:1647–1648. [PubMed: 9401319]
8. Pearl PL, Weiss RE, Stein MA. Medical mimics. Medical and neurological conditions simulating ADHD. Ann N Y Acad Sci. 2001; 931:97–112. [PubMed: 11462759]
9. Aiello DP, DuPlessis AJ, Pattishall EG 3rd, Kulin HE. Thyroid storm presenting with coma and seizures in a 3-year-old girl. Clin Pediatr (Phila). 1989; 28:571–574. [PubMed: 2582697]
10. Hsiao FC, Hung YJ, Hsieh CH, Wu LY, Shih KC, He CT. Abdominal pain and multi-organ dysfunction syndrome in a young woman. Am J Med Sci. 2007; 334:399–401. [PubMed: 18004097]
11. Landgraf L, Grubina R, Chinsky J. Altered mental status in a 16-year-old girl: the calm before the storm. Clin Pediatr (Phila). 2008; 47:720–724. [PubMed: 18698102]
12. Lee TG, Ha CK, Lim BH. Thyroid storm presenting as status epilepticus and stroke. Postgrad Med J. 1997; 73:61. [PubMed: 9039420]
13. Miller JD, Quillian W, Cleveland WW. Nonfamilial hypokalemic periodic paralysis and thyrotoxicosis in a 16-year-old male. Pediatrics. 1997; 100(3 pt 1):412. [PubMed: 9282719]
14. Rosenthal FD, Jones C, Lewis SI. Thyrotoxic vomiting. BMJ. 1976; 2:209–211. [PubMed: 974494]
15. Safe AF, Griffiths KD, Maxwell RT. Thyrotoxic crisis presenting as status epilepticus. Postgrad Med J. 1990; 66:150–152. [PubMed: 2349191]
16. Ureta-Raroque SS, Abramo TJ. Adolescent female patient with shock unresponsive to usual resuscitative therapy. Pediatr Emerg Care. 1997; 13:274–276. [PubMed: 9291518]
17. Woolston JL, Caracansi A. Case study: missed diagnosis and mistreatment of unrecognized comorbid Graves disease. J Am Acad Child Adolesc Psychiatry. 1999; 38:861–864. [PubMed: 10405504]
18. Goldyn AK, Eugster EA, Nebesio TD. Serendipitous identification of Graves' disease in identical twins with poly-dipsia. J Pediatr Endocrinol Metab. 2010; 23:1335–1337. [PubMed: 21714468]
19. Loomba-Albrecht LA, Bremer AA, Styne DM, Glaser NS. High frequency of cardiac and behavioral complaints as presenting symptoms of hyperthyroidism in children. J Pediatr Endocrinol Metab. 2011; 24:209–213. [PubMed: 21648295]
20. Centers for Disease Control and Prevention. [Accessed May 5, 2011.] State-based prevalence data of ADHD diagnosis. 2009. http://www.cdc.gov/ncbddd/adhd/prevalence.html

Table 1

Common Reported Symptoms in Children With Graves Disease

Symptom	No. of Patients (% of Total)
Palpitations/rapid heart rate	37 (48.7)
Temperature intolerance	36 (47.4)
Increased appetite	30 (39.5)
Weight loss or poor weight gain	30 (39.5)
Neck enlargement/goiter	27 (35.5)
Hyperactivity	24 (31.6)
Difficulty concentrating	21 (27.6)
Increased stool frequency	20 (26.3)
Sleep disturbance	20 (26.3)
Fatigue	19 (25.0)
Eye changes	17 (22.4)
Anxiety	15 (19.7)
Headache	14 (18.4)
Increased thirst	14 (18.4)
Jittery or restless	14 (18.4
Neck, throat pain, or difficulty swallowing	13 (17.1)
Increased urination	12 (15.8)
Mood changes	12 (15.8)
Excessive sweating	10 (13.2)
Nausea/vomiting	10 (13.2)
Respiratory symptoms	9 (11.8)
Abdominal pain	8 (10.5)
Abnormal menses	8 (10.5)

Table 2

Studies/Procedures Performed Prior to the Diagnosis of Graves Disease

Study/Procedure	Patients (% of Total)	Estimated Cost to Patient ($)
Computed axial tomography (CT) of head and neck	5 (6.6)	932.40
Electrocardiogram	5 (6.6)	143.25
Radiograph of chest	4 (5.3)	133.28
CT of abdomen and pelvis	3 (3.9)	1171.24
Echocardiogram	3 (3.9)	1379.75
Holter monitor	3 (3.9)	381.75
Magnetic resonance imaging (MRI) of head	3 (3.9)	2652.00
Esophagogastroduodenoscopy	2 (2.6)	7156.00
Ultrasound of kidney	2 (2.6)	510.00
Ultrasound of abdomen/pelvis	1 (1.3)	567.50
Adenoidectomy	1 (1.3)	10195.00
Bladder ultrasound	1 (1.3)	510.00
Central venous line placement	1 (1.3)	6655.00
Electroencephalogram	1 (1.3)	2248.75
Gastric emptying scan	1 (1.3)	1071.75
Hepatobiliary scan	1 (1.3)	983.25
MRI of spine	1 (1.3)	2326.24
Sleep study	1 (1.3)	1545.00
Supraventricular tachycardia ablation	1 (1.3)	14176.25
Upper gastrointestinal Imaging	1 (1.3)	491.40
Voiding cystourethrogram	1 (1.3)	420.00
Radiograph of cervical spine	1 (1.3)	206.50
Rapid strep test	1 (1.3)	49.50

Table 3

Hospital Admissions Prior to the Diagnosis of Graves Disease

Hospital Encounter	Presentation	Diagnostic Detours	Time in Hospital Before Thyroid Testing	Duration of Hospital Stay (Days)
Hospital ward	11-year-old female with tachycardia	Admitted to Pediatric Cardiology service. ECG and telemetry were obtained. Thyroid functions had been drawn shortly prior to hospitalization, and on discovery of these results, Pediatric Endocrinology was consulted.	Thyroid studies obtained before admission	2
Hospital ward	13-year-old female with abdominal pain, diarrhea, weight loss, and malnutrition	Admitted to Pediatric Gastroenterology service. Tests performed included ECG, abdominal radiograph and CT, esophagogastroduodenoscopy, stool studies, and central venous line placement for total parenteral nutrition. Antibiotics were started for presumed *Helicobacter pylori* infection.	6 days—tests drawn because of persistent tachycardia	9
Hospital ward	15-year-old female with hyperventilation and tachycardia	Presented to ER and treated with alprazolam with resolution of tachypnea. Tests included routine chemistries,[a] urine studies, lipase, creatine phosphokinase, and ECG. Tachycardia treated overnight with intravenous fluids.	1 day—tests drawn because of persistent tachycardia and diaphoresis	3
ICU/ward	4-year-old female with status epilepticus	Presented to ER via ambulance after receiving rectal valium, lorazepam, and fosphenytoin for prolonged seizure. Intubation was required because of apnea. On admission, routine chemistries,[a] blood gas, urine studies, and blood and urine cultures were obtained. Cardiology consulted for hypertension. Imaging studies included a chest radiograph, renal ultrasound, echocardiogram, and head CT. Initially started on phenytoin for seizures and captopril and propranolol for hypertension and tachycardia.	Obtained on the day of admission to the hospital	6
ICU/ward	9-year-old female with emesis and dehydration	Seen by primary care physician for 1 month because of weight loss. Admitted to ICU from outside hospital after 2 days of severe vomiting and dehydration. Routine chemistries[a] and blood and urine cultures obtained, with results of previous thyroid testing subsequently discovered.	Thyroid studies obtained shortly before admission	3
ICU/ward	17-year-old female with difficulty walking and paresthesias	Seen by primary care physician and then sent to ER and admitted to ICU. Initial tests included hemoglobin A1c, rapid strep test, routine chemistries, urine studies, ECG, and chest radiograph.	Obtained on the day of admission to the hospital	5

Abbreviations: ECG, electrocardiogram; CT, computed tomography; ER, emergency room; ICU, intensive care unit. a Routine chemistries include complete blood count and comprehensive metabolic profile.