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Case Report

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Perioperative Care of a Child With Hyperthyroidism

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Abstract

In pediatric-aged patients, hyperthyroidism generally results from the autoimmune disorder, Graves' disease (GD). Excessive levels of thyroid hormones (triiodothyronine and thyroxine) result in irritability, emotional lability, nervousness, tremors, palpitations, tachycardia, and arrhythmias. The risk of morbidity and mortality is increased when surgical intervention is required in patients with hyperthyroidism due to the potential for the development of thyroid storm (TS). A 3-year, 1-month-old child with a past medical history of GD presented for total thyroidectomy when pharmacologic control with methimazole was not feasible due to intolerance following development of a serum sickness-like illness. Prior to surgery, his thyrotoxicosis symptoms worsened with fever, tachycardia, diaphoresis, and hypertension. He subsequently developed TS and was admitted to the pediatric intensive care unit where management included hydrocortisone, potassium iodide, and β-adrenergic blockade with esmolol and propranolol. Thyroid studies improved prior to surgery, and a total thyroidectomy was successfully completed. Corticosteroid therapy was slowly tapered as an outpatient, and he was discharged home on hospital day 9. Following discharge, his signs and symptoms of thyrotoxicosis resolved, and he was started on oral levothyroxine replacement therapy. The remainder of his postoperative and post-discharge course were unremarkable. Only two case reports of perioperative pediatric TS have been published in the past 20 years. Our case serves as an important reminder of the signs of TS in children and to outline the treatment options in a pediatric patient, especially in those unable to tolerate first-line pharmacologic therapies such as methimazole or propylthiouracil.

Keywords: Hyperthyroidism; Graves' disease; Thyrotoxicosis; Thyroid storm; Pediatric anesthesiology

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Introduction

Hyperthyroidism generally results from overactivity of the thyroid gland, leading to excessive thyroid hormone (triiodothyronine (T3) and thyroxine (T4)) release. In both adults and children, Graves' disease (GD), an autoimmune disorder, is the most common etiology of hyperthyroidism [1]. Specifically, GD is responsible for 96% of cases of pediatric hyperthyroidism and is characterized by thyroid-stimulating hormone receptor autoantibodies (TRAbs) which stimulate thyroid hormone production [2, 3]. Other potential etiologies of hyperthyroidism in children include thyroxine over-replacement therapy in children with hypothyroidism, medications, and toxic multinodular goiters [4].

Early symptoms of hyperthyroidism in children and adolescents include irritability, emotional lability, nervousness, tremors, diarrhea, and palpitations [2, 3]. A diffuse hyperfunctional goiter manifested as a neck mass, moist skin, weight changes, brisk reflexes, and tongue fasciculations may also be present [1, 2]. Additionally, the pediatric population often presents with a decline in academic performance or an acceleration of growth with a co-existing delay in puberty [2]. Thyrotoxicosis specifically refers to a constellation of clinical signs and symptoms resulting from the end-organ effects of thyroid hormones including tachycardia, delirium, altered mental status, muscle weakness, atrial fibrillation, congestive heart failure, thromboembolic disease, cardiovascular collapse, and death [2]. In the pediatric population, symptoms of hyperthyroidism and thyrotoxicosis can be challenging to identify and are often mistaken for behavioral disorders such as attention deficit hyperactivity disorder (ADHD) [3, 4].

Patients with hyperthyroidism may require anesthetic care during surgical therapy to treat the primary disease process, for conditions that occur as a sequela of hyperthyroidism, or for unrelated conditions. Regardless of the surgical indication, when surgical intervention is required in this patient population, there is an increased risk for morbidity and mortality related to the hyperthyroid state and the potential for the development of thyroid storm (TS) [5-8]. As TS can ultimately lead to cardiovascular collapse and death, appropriate preoperative identification of the hyperthyroid state, preoperative management strategies, and perioperative protocols are recommended. To date, there are a limited number of reports discussing the perioperative management of pediatric patients with hyperthyroidism.

We present a 3-year-old child with GD and hyperthyroidism who presented for total thyroidectomy after medical ther-

apy failed to control his hyperthyroid state. The basic pathophysiology of hyperthyroidism is presented, end-organ effects are reviewed, and tenets of perioperative care outlined.

The review and presentation of this case followed the guidelines set by the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio).

Case Report

Investigations

The patient was a 3-year, 1-month-old, 14.4 kg boy with a past medical history of GD who presented for total thyroidectomy secondary to methimazole intolerance. Prior to surgery, the patient's GD was being managed with methimazole (5 mg PO every day) and atenolol (16 mg PO every day). However, he developed intolerance to methimazole, characterized by an urticarial rash, fever, and hand swelling that occurred 2 weeks after the initiation of therapy. At that time, the patient presented to the emergency department (ED) with hand swelling and hives. Workup in the ED revealed a probable serum sickness-like reaction, and endocrinology recommended a short course of high-dose corticosteroid therapy. In the ED, he was also tachycardic to 147 beats/min (bpm) and hypertensive to 119/50 mm Hg; however, TS was not suspected as thyroid studies were improved from the time of diagnosis: free T4 2.6 ng/dL (normal range: 0.7 - 2.1 ng/dL), total T3 236 ng/dL (normal range: 99 - 220 ng/dL), thyroid-stimulating hormone (TSH) < 0.015 µIU/mL (normal range: 0.6 - 4.5 µIU/mL). Liver function tests were elevated: aspartate aminotransferase (AST) 89 IU/L (normal range: 15 - 50 IU/L), alanine aminotransferase (ALT) 90 IU/L (normal range: < 36 IU/L), and methimazole therapy was discontinued. After being administered a single dose of prednisolone (15 mg PO), the patient was discharged with a 7-day course of oral corticosteroids (prednisolone 15 mg PO QD). Follow-up included close outpatient monitoring for signs of worsening hyperthyroidism with the plan to then institute therapy with oral potassium iodide solution. Three days later, he returned to the ED with fatigue, left arm pain, jitteriness, weakness, and a limp, preventing him from bearing weight or using his extremities. He was afebrile; however, the rash persisted. Tachycardia continued along with diaphoresis at night, migratory arthralgias, and continued left knee swelling. Due to the high risk of TS, the patient was scheduled for total thyroidectomy the following week and started on potassium iodide (195 mg TID PO for 7 days). The following day, the patient was seen by a local orthopedic surgeon for a second opinion of his left knee and arm, and his symptoms were deemed unrelated to an injury. That night, his migratory arthralgias and left knee swelling continued to worsen. He eventually developed a fever of 100.4 °F with worsening tachycardia, and he was advised to return to the ED due to concern for TS. In the ED, the patient presented with a fever of 101 °F, tachycardia to 180 bpm, and a systolic blood pressure > 130 mm Hg. He was given fluids and a dose of intravenous (IV) esmolol (250 µg/kg). Labs were notable for suppressed TSH < 0.015 µIU/mL (normal range: 0.6 - 4.5 µIU/mL), elevated free T4 4.5 ng/dL (normal range: 0.7 - 2.1 ng/dL), elevated total T3 590 ng/dL (normal range: 99 - 220 ng/dL), white blood cell count of 22.2 × 10^3/µL (normal: 6.0 - 17.0 × 10^3/µL), and thrombocytosis with a platelet count of 556 × 10^3/µL (normal: 142 - 508 × 10^3/µL). Given the ongoing thyrotoxicosis associated with fever, hypertension, and tachycardia, he was subsequently admitted to the pediatric intensive care unit (PICU) for management of suspected TS. Hydrocortisone (50 mg/m^2 IV every 8 h) and potassium iodide (250 mg PO every 8 h) were started. An esmolol infusion was started and titrated up to 225 µg/kg/min to control the tachycardia and hypertension. The rheumatology service started the patient on naproxen (150 mg PO every 12 h) due to the arthralgias and ongoing concern for a serum sickness-like reaction. Oral propranolol was also initiated and increased to control his tachycardia as the esmolol infusion was weaned. On hospital day 2, the esmolol infusion was titrated to 300 µg/kg/min, potassium iodide was increased to 350 mg PO every 8 h, and the propranolol dose was increased to 0.5 mg/kg PO every 6 h. An echocardiogram at that time was significant for hyperdynamic left ventricular systolic function, trivial aortic valve regurgitation, and mild mitral valve regurgitation. Esmolol was discontinued on hospital day 3, and propranolol was continued at 0.5 mg/kg PO every 6 h. Ultrasound of the thyroid done on hospital day 4 was significant for an enlarged hypervascular gland in the setting of diffuse thyroiditis. The patient was scheduled for the operating room (OR) on hospital day 5.

Diagnosis

Preoperatively, the patient's temperature was 97.8 °F, heart rate (HR) was 114 bpm, respirations were 30 breaths/min, blood pressure (BP) was 125/74 mm Hg, and oxygen saturation was 100%. Airway, cardiac, and respiratory examinations were unremarkable. The thyroid gland was not noted to be significantly enlarged on physical examination and was not impinging on the airway. Preoperative labs revealed improved thyrotoxicosis: TSH < 0.015 µIU/mL, total T3 182 ng/dL, free T4 2.8 ng/dL. The patient was assigned an American Society of Anesthesiologists physical status class 3. Twenty-four hours prior to the OR, the naproxen was held, and on the day of surgery, the potassium iodide was discontinued. The patient was transported to the OR and routine American Society of Anesthesiologists monitors were placed. Premedication included IV midazolam (2 mg). Anesthesia was induced by the IV administration of incremental doses of propofol (total dose of 6 mg/kg), lidocaine (1 mg/kg), and fentanyl (2 µg/kg). After spraying the trachea with 1 mL of 4% lidocaine, the trachea was intubated without neuromuscular blockade with a 4.0 mm cuffed endotracheal tube. A direct laryngoscopy was performed, and electromyography (EMG) electrodes were placed directly onto the vocal cords to allow for recurrent laryngeal nerve monitoring via a neural integrity monitor. Following the induction of anesthesia, an arterial cannula and a second peripheral IV cannula were placed. Maintenance anesthesia was provided by sevoflurane (expired concentration 1.7-2.6%) in air and oxygen, fentanyl (total intraoperative dose of 7 µg/kg), and a remifentanil infusion (0.2 - 0.4 µg/kg/min). Intraopera-

tively, the HR varied from 102 to 138 bpm with a BP of 72 - 83/30 - 40 mm Hg. Additional medications administered intraoperatively included dexmedetomidine (8 µg), ondansetron (2 mg) for prevention of postoperative nausea and vomiting, morphine (2 mg), and acetaminophen (250 mg IV) for postoperative analgesia. Intraoperative blood loss was less than 30 mL. Intraoperative fluids included lactated Ringers (525 mL) and 5% albumin (150 mL). Total intraoperative time was 2 h 45 min. At the completion of the surgical procedure, the patient's trachea was extubated at a deep plane of anesthesia during spontaneous ventilation. The patient was transported to the post-anesthesia care unit (PACU) with spontaneous respirations.

Follow-up and outcomes

The patient tolerated the procedure well and was transferred to the inpatient ward from the PACU. One day following surgery, his tachycardia continued to improve. T3 down-trended and T4 did not increase further: TSH < 0.015 µIU/mL, total T3 74 ng/dL, and free T4 3.1 ng/dL. Oral propranolol was continued postoperatively and then transitioned to oral atenolol (16 mg PO every day). HR and BP continued to improve postoperatively without the need for pharmacologic control. Serum calcium was monitored following surgery and oral supplementation was discontinued on postoperative day 2. Prior to discharge, thyroid studies remained controlled: TSH < 0.015 µIU/mL (normal range: 0.6 - 4.5 µIU/mL), total T3 87 ng/dL (normal range: 99 - 220 ng/dL), and T4 2.3 ng/dL (normal range: 0.7 - 2.1 ng/dL). Corticosteroid therapy was weaned and then slowly tapered as an outpatient. He was discharged home on hospital day 9. Following discharge, the signs and symptoms of TS resolved, and he was eventually started on oral levothyroxine replacement therapy (62.5 µg PO daily). The remainder of his postoperative and post-discharge course were unremarkable.

Discussion

The overproduction of T3 and T4 from the thyroid gland may stem from a variety of underlying mechanisms. GD is the most common etiology of hyperthyroidism across all age groups and genders and has been shown to have a female predominance [1, 2, 9-12]. GD is driven by a T-cell-mediated process, where T cells evoke B-cell dysregulation via cytokine-mediated inflammation and remodeling, ultimately resulting in the production of antibodies targeting TSH receptors [13]. The formation of TRAbs results in the overproduction of T3 and T4 via follicular cell growth [3]. Although not fully resolved, the development of GD is thought to involve the interplay of genetic, environmental, and individual immunological factors. Individual genetic variation and susceptibility has been demonstrated by the potential association of specific genotypes with the pathogenesis of the disease [3, 14].

GD remains rare in the pediatric population, with children accounting for only 1-5% of all cases of hyperthyroidism across all age ranges [15]. In a 2015 epidemiological study including patients ranging in age from 6 months to 17 years in France, the nationwide incidence was 4.58/100,000 person-years [11]. A retrospective study from Denmark from 1998 to 2002 reported an incidence of 1.58/100,000 person-years [12]. Despite its rarity, the incidence appears to be increasing in children under 15 years of age [12]. In younger children, increased severity of GD is often observed likely due to delays in diagnosis and higher TRAb levels in comparison to their adult counterparts [1, 3]. Other etiologies of hyperthyroidism seen in the pediatric population include toxic multinodular goiters, levothyroxine over-replacement, the transient hyperthyroid phase of Hashimoto's thyroiditis, or congenital hyperthyroidism secondary to the transplacental passage of TRAbs from the mother to the fetus [1, 2, 4].

As a result of the negative hormonal feedback pathway, laboratory findings in GD are significant for suppressed TSH levels and elevated free T3 and T4 levels. Excessive stimulation of the thyroid gland may result in the formation of a diffuse goiter, which can sometimes be evident on physical exam [1, 4]. Subclinical hyperthyroidism may also exist, defined by T3 and T4 levels in the normal range despite TSH concentrations below the lower limit [4]. In order to confirm the diagnosis of GD, thyroid-stimulating immunoglobulin (TSI) or TRAb levels must be tested [2]. In children, the general symptoms of hyperthyroidism often make the diagnosis of GD difficult to discern given the overlap in symptomology with behavioral disorders [2, 3]. As evident in the case presented, if uncontrolled, hyperthyroidism may progress to a TS, a state defined by thyrotoxicosis that can ultimately result in cardiovascular collapse and death [10, 16].

Pharmacologic therapies remain the first-line treatment for GD. In children, methimazole, first approved in 1950, is the preferred antithyroid medication given its efficacy and adverse effect profile [2, 17]. It controls thyroid hormone synthesis via inhibition of the organification and coupling of iodothyronines [2]. Propylthiouracil (PTU) is another antithyroid medication, which in addition to blocking thyroid peroxidase like methimazole, additionally inhibits tetraiodothyronine 5′ deiodinase, preventing the peripheral conversion of T4 to T3 [18]. PTU was first approved for the treatment of hyperthyroidism in 1947 and was commonly used to treat GD in children [19, 20]. However, given accumulating clinical evidence regarding its potential to cause hepatoxicity, its use as a first-line agent was no longer recommended, and in 2009, the FDA added a black box warning highlighting its potential adverse effects [19, 20].

In addition to medications that inhibit the synthesis of the thyroid hormones, β-adrenergic antagonists such as atenolol, esmolol or propranolol are frequently used for symptom management, primarily heart rate control [2]. Permanent treatment of GD, including radioactive iodine treatment (RAI) or thyroidectomy, is recommended for children who fail to achieve control with first-line pharmacologic agents, or as evident in our case, if the patient is unable to tolerate methimazole or other antithyroid medications [2]. Our patient developed evidence of hepatotoxicity including elevated liver function tests and a serum sickness-like reaction following 2 weeks of methimazole therapy. Similar reactions to methimazole have been reported in the literature [21, 22]. The patient's serum

sickness-like illness was treated with corticosteroids while treatment of his hyperthyroidism was switched to potassium iodide with HR control provided by atenolol. Potassium iodide (SSKI) or Lugol's solution is known to control hyperthyroidism via the Wolff-Chaikoff effect, characterized by the inhibition of thyroperoxidase in the presence of excessive iodine, therefore decreasing the synthesis of thyroid hormones [23]. Although originally intended to control perioperative hyperthyroidism and minimize the risk of intraoperative storm, potassium iodide is currently employed to enhance surgical feasibility and safety, as studies have shown when given prior to thyroidectomy, it may also reduce blood flow and thereby blood loss during thyroidectomy [24]. Our patient was started on potassium iodide (195 mg TID PO) perioperatively to achieve both suppressive effects on thyroid hormone production in the absence of methimazole, as well as reduce blood flow and potentially blood loss.

One of the primary perioperative concerns related to hyperthyroidism is the development of TS. TS is characterized by a state of enhanced release of and sensitivity to thyroid hormones precipitated by infection, trauma, surgery, discontinuation of anti-thyroid medications, or following RAI treatment [2]. Precipitation of a TS in the perioperative period can have significant adverse effects on patient outcomes, including cardiovascular complications such as tachycardia, atrial fibrillation, ventricular dysfunction, heart failure, myocardial ischemia, and hypertension, as well as central nervous system (CNS) manifestations (seizures), posing an increased risk of mortality [10, 25, 26]. Furthermore, progression to TS is associated with an increased length of hospitalization and increased length of mechanical ventilation [26, 27]. Overall, the incidence of TS in hyperthyroid patients across all age groups undergoing surgery has been reported to range from 0% to 14% [28].

The most common presenting signs and symptoms of TS include tachycardia, hypertension, diarrhea, unintentional weight loss, and altered mental status [10]. In our patient, the development of TS was characterized by fever, tachycardia with an HR of 180 - 190 bpm, and hypertension with a systolic blood pressure > 130 mm Hg. Although there are no pediatric-specific scoring systems to aid in the diagnosis of TS, the adult scoring system developed by Burch and Warsofsky is often used [29]. Criteria of the scoring system include hyperpyrexia, mental status changes, cardiovascular decompensation, and gastrointestinal (GI)/hepatic dysfunction [2, 10, 29]. As uncontrolled thyrotoxicosis can predispose a patient to developing TS perioperatively, identification of hyperthyroidism preoperatively is crucial [3, 5, 10]. If thyrotoxicosis is suspected, further workup should be pursued prior to surgery, including thyroid function tests (TSH, T3, T4), complete blood count (CBC), and electrocardiogram (ECG) [5]. In the intraoperative and postoperative settings, appropriate differential diagnoses should also be considered, such as malignant hyperthermia, serotonin syndrome, or neuroleptic malignant syndrome, as these disease processes can often present with overlapping features [16].

In 2022, Abisad et al published the first systematic review describing TS in 45 pediatric patients (< 21 years of age) to identify common causes and the most effective treatment regimen [10]. Undiagnosed GD was the most common etiology of TS, accounting for 18.4% of cases, with 6% of the cases presenting during or after surgery. The mean age of patients with TS from all etiologies was 11.25 years, with a female-to-male ratio of 1.67:1, while those with TS secondary to GD demonstrating a female-to-male ratio of 3.28:1. Tachycardia and fever were the most common presenting signs, while other presenting symptoms included diarrhea, altered mental status, and hypertension [10]. Our patient presented with similar signs and symptoms of TS, including fever, hypertension, and tachycardia, all of which progressively worsened following his discontinuation of methimazole, necessitating the institution of oral potassium iodide therapy.

In our patient's case, TS developed in the preoperative period and was managed via hydrocortisone (50 mg/m^2 IV every 8 h), potassium iodide (250 - 350 mg PO every 8 h), esmolol (continuous IV infusion at 225 - 300 µg/kg/min), and propranolol (0.5 mg/kg PO every 6 h). Prior to his surgery, his free T4 and T3 levels were optimized, and his Burch-Wartofsky score improved from 45 to 15 - 25. On the day of surgery, the potassium iodide was discontinued, while the propranolol (0.5 mg/kg PO every 6 h) was continued. Intraoperatively, HR control was achieved with remifentanil, dexmedetomidine, and sevoflurane. Anesthetic medications with the potential to increase HR or stimulate the sympathetic nervous system (isoflurane, desflurane) were avoided. Perioperative intermittent β-adrenergic antagonist therapy was continued with the ready availability of an intraoperative esmolol infusion if needed for additional HR control. Following surgery, oral propranolol was continued before therapy was subsequently transitioned back to oral atenolol (16 mg PO every day).

According to the European Thyroid Association, the guidelines for the pharmacologic management of TS, published in 2022, involve four major components [30]. These include an antithyroid medication, a β-adrenergic antagonist, SSKI or Lugol's iodine, and corticosteroids [30]. According to the 2016 American Thyroid Association guidelines, propranolol is the β-adrenergic antagonist of choice, given its ability to block the conversion of T4 to T3 at high doses, while the Japanese Thyroid Association identifies esmolol as the agent of choice, justified by its cardioselective properties and ease of titration by IV infusion [31, 32].

Although not specific to the pediatric population, in 2021, de Mul et al published a systematic review assessing the risk of TS for different preoperative treatment options [28]. Similar to previous findings, the authors concluded that there is insufficient evidence to suggest that preoperative treatment in patients undergoing thyroidectomy protected against the development of a perioperative TS [28]. Our case serves to outline the treatment options for TS in a pediatric patient, especially in those unable to tolerate first-line pharmacologic therapies such as methimazole or PTU. Only two case reports of perioperative pediatric TS have been published in the past 20 years [7, 8].

Learning points

Hyperthyroidism results from overactivity of the thyroid gland, leading to excessive thyroid hormone (T3 and T4) release. GD, an autoimmune process, is the most common etiology of hyperthyroidism in both children and adults. Despite its rarity,

the incidence appears to be increasing in children ≤ 15 years of age. In younger children, the severity of GD is often increased likely due to delays in diagnosis and higher TRAb levels in comparison to their adult counterparts. Other etiologies of hyperthyroidism in the pediatric population include toxic multinodular goiters, levothyroxine over-replacement, the transient hyperthyroid phase of Hashimoto's thyroiditis, and congenital hyperthyroidism secondary to the transplacental passage of TRAbs. Pharmacologic control includes medications that inhibit the synthesis of the thyroid hormones (PTU or methimazole) and β-adrenergic antagonists for symptom management, primarily HR control. Permanent treatment of GD, including RAI or thyroidectomy, is recommended for children who fail to achieve control with pharmacologic agents. One of the primary perioperative concerns related to hyperthyroidism is the development of TS. Guidelines for the pharmacologic management of TS include an antithyroid medication, a β-adrenergic antagonist, SSKI, and corticosteroids.

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None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained for anesthetic care and the use of de-identified information for publication.

Author Contributions

JB: preparation of initial, subsequent, and final drafts; TG and GM: review of final draft, perioperative care of patient; JDT: concept, review of all drafts.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

ADHD: attention deficit hyperactivity disorder; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CBC: complete blood count; ECG: electrocardiogram; ED: emergency department; GD: Graves' disease; PTU: propylthiouracil; RAI: radioactive iodine treatment; T3: triiodothyronine; T4: thyroxine; TRAbs: thyroid-stimulating hormone receptor autoantibodies; TS: thyroid storm; TSH: thyroid-stimulating hormone

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