Scientific Open Access Journals
SOAJ

Advances in Critical Care Medicine

Case Report Open Access

Refractory Thyroid Storm in a Pediatric Patient

Matthias Manuel[1,2]*, Renee M. Potera[1,2], Abha Choudhary[1,2] and Jennifer Tiller[1,2]

[1]University of Texas Southwestern Medical Center, Dallas, Texas, USA

[2]Children's Medical Center, Dallas, Texas, USA

***Corresponding author: Matthias Manuel,** Email: Matthias.Manuel@utsouthwestern.edu

Received: 24 September 2020; **Accepted:** 24 December 2020; **Published:** 29 December 2020

Case Presentation

A 16-year-old female with history of hyperthyroidism presents to the emergency department (ED) with one day history of fever, fatigue, gait instability, and altered mental status (AMS). Grandfather states that earlier in the day she reported being weak and tired, and later became significantly confused with altered consciousness, prompting ED visit. Further history reveals likely non-compliance with prescribed methimazole.

Upon arrival, she is noted to be drooling, confused, mumbling incoherently, and agitated with a Glasgow Coma Scale (GCS) of 11. Vital signs are notable for fever (T=40.1°C), tachycardia (HR>170), tachypnea (RR>50), and hypertension (SBP>130mmHg). Physical exam reveals no focal neurologic deficits and her neck is supple without obvious masses or clinically enlarged thyroid gland. Other notable exam findings include oropharyngeal erythema with bilateral tonsillar exudates and copious clear frothy secretions requiring intermittent suctioning, tachycardia with bounding peripheral pulses, moist skin, mild diffuse abdominal tenderness with some guarding without organomegaly, and minimal vaginal bleeding without any evidence of a foreign body. The remainder of her exam is unremarkable.

Resuscitation is initiated with intravenous (IV) crystalloids, acetaminophen, and ceftriaxone. Laboratory tests and imaging are ordered. Lumber puncture is deferred due to clinical and hemodynamic instability. Her pregnancy test is negative, electrocardiogram (EKG) shows sinus tachycardia with QTc prolongation (QTc=475ms), point-of-care (POC) venous blood gas (VBG) reveals borderline alkalosis (pH of 7.45) with lactate of 5.37, and rapid antigen test for Group A *Streptococcus* is positive. Other significant lab results include neutropenia with agranulocytosis (WBC=0.6, ANC=0), hyponatremia ($[Na^+]$ = 127mEq/L), and elevated CRP of 11.2mg/dL. Antibiotic coverage is broadened to IV piperacillin-tazobactam and vancomycin on account of persistent fever with agranulocytosis.

Her urinalysis (UA), urine pregnancy test, liver function test (LFT), serum lipase, ethanol, acetaminophen, and salicylate, and laboratory VBG are all normal. Soft tissue neck and chest radiographs and head CT are normal, but her CT abdomen/pelvis is reported as incompletely visualized, but mildly enlarged heart, without any evidence of intra-abdominal or pelvic pathology. Subsequent brain natriuretic peptide (BNP) level is found to be elevated (766.5 pg/mL), prompting cardiology consult with echocardiogram request.

Despite initial resuscitative efforts, she remains agitated with relatively unchanged vital signs and mental status. Laboratory tests resulting later include negative respiratory viral panel, COVID-19, and toxicology screens, but her thyroid function test (TFT) shows elevated triiodothyronine (total T3=428 ng/dL) and free thyroxine (fT4=8.95 ng/dL), with suppressed thyroid stimulating hormone (TSH<0.008 μIU/mL) levels. Pediatric endocrinology is consulted and recommends starting propranolol, hydrocortisone, and saturated solution of potassium iodide (SSKI). Methimazole (MMI) is held due to agranulocytosis. She however develops hypotension after receiving 1mg of IV propranolol given over 10 minutes and requires vasopressors with good response in blood pressure. The decision is made to transport her to the ICU where she will be started on SSKI and a continuous esmolol infusion.

Discussion

The differential diagnosis of persistent high-grade fever, agitation, progressive confusion with altered sensorium in an adolescent with history of hyperthyroidism and exam findings as documented above include, but not limited to severe sepsis, meningo-encephalitis, toxic ingestion, substance abuse, pheochromocytoma, thyroid storm, psychotic disorder, neuroleptic malignant syndrome, panic disorder, hypertensive encephalopathy, and serotonin syndrome [1].

For our index patient, a diagnosis of thyroid storm (TS) or thyrotoxic crisis was favored based on her clinical presentation and history of hyperthyroidism, supported by her TFT results. As per the widely adopted Burch and Wartofsky diagnostic point scale for thyroid storm, our patient had a score of > 90, exceeding the minimum score of 45 required for suspected TS diagnosis [2].

Upon ICU admission, patient was started on SSKI, cholestyramine, and low dose esmolol infusion which was complicated by bradycardic cardiac arrest with complete AV dissociation on telemetry and acute kidney injury. Esmolol was discontinued, she was immediately intubated and resuscitated with return of spontaneous circulation (ROSC) within six minutes of resuscitative efforts. Post-arrest echocardiography showed moderate to severe biventricular dysfunction, manifesting clinically as hypotension requiring brief infusions of norepinephrine and vasopressin.

Despite these interventions, she continued to have persistent tachycardia, hyperpyrexia, and hemodynamic instability. Follow-up labs also showed low serum levels of magnesium and calcium, and persistently elevated T3 and T4 levels. She required cooling blankets, scheduled antipyretics, and electrolyte supplementation. Following improvement in her hemodynamic function, she was started on atenolol, augmented with isradipine for BP>140/90 mmHg. Hematology was consulted and a collaborative decision was made to start filgrastim for agranulocytosis and therapeutic plasma exchange (PLEX) for refractory thyroid storm [3-6]. After two PLEX sessions on days 2-3 of ICU admission (DOA 2-3), her clinical status and laboratory indices improved, and she was successfully extubated on DOA 4.

In the setting of possible methimazole-induced agranulocytosis, it was decided that patient will benefit from thyroidectomy and on Day 10 of admission she underwent total thyroidectomy and was started on Levothyroxine. Antibiotics and all other medications were later discontinued following negative culture results, improvement in ANC and thyroid hormone levels, and hemodynamic stability. She was later discharged home in a stable clinical state on levothyroxine and calcium supplements after 14 days of hospitalization. She continues to do well during her recent outpatient follow-up visit.

Thyroid storm is a rare but life-threatening endocrine emergency with extreme multisystem manifestations of hyperthyroidism. Its incidence in children is not clear, but about 0.2 - 0.8 per 100,000 persons-per-year has been reported in the general population, with 10 – 25% mortality. Incidence of TS in hospitalized patients with thyrotoxicosis can be as high as 16% and mortality without treatment approaches 80-100% [1,7-11].

TS is most commonly seen in patients with Graves' hyperthyroidism, like the index patient; but it may complicate thyrotoxicosis of any etiology [9]. Although the pathophysiology is not fully understood, all major organs of the body are affected by the extremely high thyroid hormone levels, which bind to end-organ nuclear receptors eliciting a cascade of events that result in symptoms through upregulation of β_1-adrenergic receptors, production of cytokines, and exaggerated hypermetabolic states with increased oxygen consumption. End-organ effects are mediated by T3, since most of T4 is converted to T3 peripherally.

Infection remains the most common trigger of TS in patients with thyrotoxicosis [8]. This was the suspected precipitant in our patient who had a positive streptococcus pharyngitis screen, in the setting of medication (methimazole) non-compliance. Other identified triggers include, trauma, surgery (especially thyroidectomy), pregnancy or parturition, diabetic ketoacidosis, medications (amiodarone, RAI: radioactive-iodine ablation), myocardial infarction, antithyroid medication cessation, and general stressors. In about 20-25% of cases no acute precipitant is identified [1,7-10].

Clinical manifestations are usually non-specific; therefore, a high index of suspicion is required to avoid significant delays in diagnosis, especially in patients with a history of hyperthyroidism. Notable symptoms and exam findings in keeping with TS in our patient include generalized fatigue, hyperpyrexia despite antipyretics, neuropsychiatric (CNS) manifestations (agitation, confusion, and delirium with AMS), nausea, vomiting, abdominal tenderness, cardiovascular dysfunction (persistent tachycardia, cardiac failure), and sweaty moist skin at baseline. Other manifestations of TS may include features of hepatotoxicity (jaundice), tachyarrhythmias, features of congestive heart failure, etc.

Definite diagnosis of TS is made based on laboratory evidence of elevated T3 and fT4 and decreased TSH levels in the presence of ≥1 CNS and ≥1 non-CNS manifestations.[1] End-organ effects of TS may be assessed with other diagnostic tests such as CBC with differentials, electrolytes, LFT, renal function test, EKG, brain natriuretic peptide (BNP), echocardiography, and cortisol level. Other diagnostic tests and imaging modalities may be performed as needed to explore possible triggers or to rule out other differentials. Adolescent females should have urine or serum pregnancy test done.

Goals of care typically in the ICU setting can be broadly categorized into supportive and specific therapy. Acute care involves prompt assessment of airway, breathing, circulation, disability, and examination (ABCDE); while supportive care involves cooling measures, IVFs for circulatory support, ventilatory support, electrolyte replacement, sedatives for profound agitation, nutritional support, treatment of precipitating factors and end-organ complication, etc. Specific therapy goals are summarized with '**five Bs**': **b**lock hormone synthesis (antithyroid medications, thionamides: MMI - first line for children, PTU – if MMI is contraindicated or in pregnancy), **b**lock hormone release (iodine: SSKI, Lugol's iodine - administer at least an hour after thionamides to avoid iodination of tyrosine residue), **b**lock peripheral conversion of T4 into T3 (high-dose PTU, propranolol, corticosteroid, and rarely with amiodarone), **b**lock β_1-adrenergic receptors (propranolol, esmolol, atenolol, etc.), and **b**lock enterohepatic circulation (Cholestyramine).[9] Corticosteroids (hydrocortisone or dexamethasone) also find relevance in adrenal axis dysfunction seen in thyrotoxicosis. RAI may be used after a course of thionamides, while thyroidectomy remains the last resort for refractory cases.

Other emerging treatment options for refractory TS include plasmapheresis (PLEX: as therapy or in preparation for surgery to reduce circulating thyroid hormone levels), charcoal hemoperfusion, use of biologics such as Rituximab for immune-mediated thyrotoxic states.[9,12]

Lessons for Clinicians

- TS is a rare but life-threatening multisystem endocrine emergency associated with significant morbidity and mortality.
- Clinical manifestations may be non-specific; however, prompt recognition and timely intervention is crucial to avoid severe multi-organ complications and significant mortality.
- While supportive care and specific antithyroid therapy remain the cornerstone of treatment, it is crucial to search for precipitating factors of TS and treat concurrently. Acute infections being the most common precipitant
- Consult relevant subspecialties. A collaborative effort is needed to survive this storm. Do not face the storm all by yourself!

References

1. Idrose AM. Acute and emergency care for thyrotoxicosis and thyroid storm. Acute Med Surg. 2015; 2:147-157.
2. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am. 1993; 22:263-277.
3. Muller C, Perrin P, Faller B, Richter S, Chantrel F. Role of Plasma Exchange in the Thyroid Storm. Ther Apher Dial. 2011; 15:522-531.
4. Ba J-H, Wu B-Q, Wang Y-H, Shi Y-F. Therapeutic plasma exchange and continuous renal replacement therapy for severe hyperthyroidism and multi-organ failure: A case report. World J Clin Cases. 2019; 7:500-507.
5. McGonigle AM, Tobian AAR, Zink JL, King KE. Perfect storm: Therapeutic plasma exchange for a patient with thyroid storm. J Clin Apheresis. 2018; 33:113-116.
6. Carhill A, Gutierrez A, Lakhia R, Nalini R. Surviving the storm: two cases of thyroid storm successfully treated with plasmapheresis. BMJ Case Rep. 2012.
7. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016; 26:1343-1421.
8. Srinivasan S, Misra M. Hyperthyroidism in Children. Pediatr Rev. 2015; 36:239-248.
9. Carroll R, Matfin G. Endocrine and metabolic emergencies: thyroid storm. Ther Adv Endocrinol Metab. 2010; 1:139-145.
10. Ross DS, Cooper DS, Mulder JE. Thyroid storm - UpToDate. 2019.
11. Akamizu T. Thyroid Storm: A Japanese Perspective. Thyroid. 2018; 28:32-40.
12. Minamitani K, Sato H, Ohye H, Harada S, Arisaka O. Guidelines for the treatment of childhood-onset Graves' disease in Japan, 2016. Clin Pediatr Endocrinol. 2017; 26:29-62.