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Thyroid storm following radioactive iodine (RAI) therapy for pediatric graves disease

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 11
Final Diagnosis: Thyroid storm
Symptoms: Diarrhea • tachycardia • tachypnea • tremor • wheezing
Medication: —
Clinical Procedure: —
Specialty: —

Objective: Rare disease





Background: A growing number of pediatric endocrinologists treat Graves disease with radioactive iodine (RAI) therapy due to the typically definitive nature of I-131 therapy. Given the published benefits and perceived low risks of RAI when compared to surgery or long-term anti-thyroid medication, the trend towards therapy with RAI is likely to continue. Nevertheless, RAI is not without significant risk.

Case Report: An 11-year-old girl with newly diagnosed Graves disease received RAI for definitive treatment of her hyperthyroidism. Within 24 hours of receiving I-131, she developed increasing sleepiness and eventually became unresponsive. Upon arrival at the emergency department she had a tonic-clonic seizure and was diagnosed with thyroid storm. Despite best efforts to manage her hyperthyroidism, she suffered a stroke of the left cerebral hemisphere that left her with persistent neurological deficits.

Conclusions: Although thyroid storm after thyroid ablation is rare, the significant morbidity and potential mortality of pediatric thyroid storm warrant further studies to determine if children with markedly elevated thyroid hormone concentrations at diagnosis should receive prolonged pretreatment with anti-thyroid drugs. While such an approach may reduce the efficacy of I-131 ablation, it can also reduce and hopefully eliminate the risk of post-ablative thyroid storm.

MeSH Keywords: Graves Disease • Hyperthyroidism • Thyroid Storm • Pediatrics • Iodine Radioisotopes

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Background

Graves disease results from the inappropriate production of thyroid-stimulating immunoglobulins (TSI), binding of TSI to thyroid-stimulating hormone receptors, and the resultant secretion of excess thyroid hormone. A growing number of pediatric endocrinologists treat Graves disease with radioactive iodine (RAI) therapy due to the typically definitive nature of iodine-131 (I-131). Given the published benefits and perceived low risks of RAI when compared to surgery or long-term anti-thyroid medication, the trend towards therapy with RAI is likely to continue. However, RAI is not without significant risk. Herein, we report a case of thyroid storm presenting 1 day after RAI in an 11-year-old with recent-onset Graves disease.

Case Report

An 11-year-old Caucasian girl was evaluated in an outside emergency department after a 4-day history of tachycardia, shortness of breath, wheezing, and tachypnea. She was treated for presumed pneumonia and started on antibiotics. After 24 hours of persistent tachycardia (160–190 beats per minute) she was transferred to our academic institution for further treatment and evaluation. Review of systems revealed no heat intolerance, diaphoresis, tremor, weight loss, difficulty sleeping, or fatigue, but she did report recent onset of diarrhea and decreased oral intake. Notably, the patient felt that her tachycardia had begun only 4 days prior to admission.

Upon her arrival, thyroid function tests were performed and revealed a markedly elevated free T4 (>6 ng/dL), elevated T3 (>500 ng/dL), and suppressed TSH (<0.01 mIU/L). Review of her records revealed that a TSH measured by her primary care doctor 3 months before admission was suppressed (TSH <0.08 mIU/L).

Pertinent findings on her initial physical exam included blood pressure (BP) 136/67, heart rate (HR) 132, temperature 36.6°C, height 144 cm (20th percentile), and weight 36 kg (20th percentile). There was no proptosis or exophthalmos. She had mild flattening of the face and micrognathia. Her thyroid was diffusely enlarged, smooth, and firm with no palpable nodules. A thyroid bruit was not appreciated. She had slight tremor of her hands at rest.

Given her thyroid function studies and physical exam findings, she was presumptively diagnosed with Graves disease and was prescribed propranolol 10 mg 4 times daily (1.25 mg/kg/day) and propylthiouracil (PTU) 50 mg 3 times daily (4.7 mg/kg/day). Notably, this case occurred prior to the Food and Drug Administration's (FDA) release of a black box warning for PTU secondary to liver toxicity. Thyroid autoantibody

assays were ordered and she was discharged from the hospital the following day with instructions to follow up with Pediatric Endocrinology.

Thyroid autoantibody testing confirmed the diagnosis of Graves disease. Thyroid binding inhibiting immunoglobulin assay (TBII) was markedly elevated at 51% (16% or less), thyroid-stimulating immunoglobulin (TSI) assay was normal at 98% (0–129%), thyroid peroxidase antibodies were elevated at 835.1 IU/mL (<3.9), and thyroglobulin antibodies were negative ($<1:100$). A thyroid uptake scan was not performed given the unequivocal laboratory values.

The patient returned to the Pediatric Endocrinology clinic 4 days after hospital discharge. The family noted increasing difficulty administering 2 different medications multiple times per day. As such, the relative risks and benefits of continued anti-thyroid medication versus surgery versus RAI were discussed. Because the patient and her mother eagerly sought more definitive therapy, she was referred to our radiation oncology colleagues and scheduled for RAI ablation. She remained on propranolol for treatment of her symptoms, but PTU was discontinued.

Eight days later, the patient received 10 mCi of I-131 as an oral tablet for thyroid ablation. Vital signs measured prior to ablation revealed temperature of 36.2°C, HR 101, and BP 129/55. The following morning she reported being unusually sleepy and became increasingly unresponsive over the next 2–3 hours. She was transported to the closest emergency department and was intubated upon arrival due to hypopnea. Shortly after intubation, she had a tonic-clonic seizure and was given 1 mg intravenous lorazepam. Blood samples drawn just prior to her seizure demonstrated serum glucose 38 mg/dL (treated with intravenous dextrose) and potassium 6.5 mmol/L (treated with sodium polystyrene sulfonate and furosemide). A computed tomography scan of her head was performed and was normal. She was transferred to the Pediatric Intensive Care Unit at our institution for additional evaluation and treatment.

Pediatric Endocrinology was again consulted for management of her Graves disease and evaluation for possible thyroid storm. Pertinent findings on physical exam included temperature 37.2°C, HR 158, BP 96/57, and endotracheal tube in place. She was not sedated, but was not fully coherent. Her thyroid remained diffusely enlarged and firm without bruit. She had tachycardia with no murmur, and was noted to have mild upper right extremity weakness.

Repeat thyroid function tests revealed persistently elevated free T4 (>6 ng/dL), elevated T3 (>500 ng/dL), and suppressed TSH (<0.01 mIU/L). Serum cortisol and ACTH levels were measured to assess for adrenal insufficiency and stress-dose

hydrocortisone was provided given the history of hypoglycemia and hypotension and the known association of relative adrenal insufficiency with thyrotoxicosis [1]. Given the combination of her Graves disease, I-131 therapy, and seizure, a presumptive diagnosis of thyroid storm was considered, although she was afebrile, somewhat hypotensive, and had only mild tachycardia.

Low-dose intravenous propranolol was initiated with plans to titrate as needed to control her heart rate. MRI was obtained to evaluate her right extremity weakness and revealed diffuse, abnormally increased FLAIR signal with associated cerebral edema throughout the left and right cerebral cortex and subcortical gray matter, as well as patchy areas of involvement in the left parietal lobe, left parafalcine occipital lobe, left and right temporal lobe, and right uncus and parahippocampal gyrus. The following day the patient became febrile and had a second seizure. Hydrocortisone (100 mg intravenous every 6 hours), propranolol (150 mg every 8 hours), PTU (150 mg every 6 hours), and supersaturated Potassium Iodide (SSKI) (6 drops orally every 6 hours) were given for the treatment of thyroid storm.

Ten days after her admission, she developed elevated liver enzyme concentrations and was transitioned from PTU to methimazole. Her clinical status improved rapidly and she was extubated 48 hours after admission. She continued to have right-sided weakness and aphasia that improved throughout the remainder of her admission. She was discharged home approximately 1 month after her I-131 ablation with free T4 2.77 ng/dL (0.93–1.7) and T3 245 ng/dL (80–200). Notably, she developed additional elevations of her liver enzyme concentrations while taking methimazole and eventually had to discontinue use of both PTU and methimazole. Her T4 and T3 concentrations remained markedly elevated for nearly 2 months before demonstrating a trend towards normalization. She finally achieved elevation of her TSH at 8 months after ablation.

Additional review of her imaging confirmed that the stroke affected the middle cerebral artery distribution of her left cerebral hemisphere. During the first year after her thyroid storm she required therapy for a seizure disorder as well as occupational, speech, and physical therapy. Five years after her thyroid storm, she continued to have some difficulty with memory and data integration but continues to make progress academically, socially, and developmentally.

Discussion

Thyroid storm is rare in the pediatric population, with a frequency of 0.1–3.0 per 100 000 [2]. Precipitating factors include sepsis, surgery, induction of anesthesia, RAI therapy, excessive

thyroid hormone ingestion, rapid withdrawal or discontinuation of antithyroid drugs, diabetic ketoacidosis, direct trauma to or vigorous palpation of the thyroid, toxemia of pregnancy and labor or molar pregnancy, and numerous drugs, including pseudoephedrine, salicylates, nonsteroidal anti-inflammatory drugs, and chemotherapy agents [3].

Previous cases of pediatric thyroid storm have been reported 2–8 days after RAI therapy [4,5]. In 1978, Hayek published a case in which a 10-year-old girl with Down syndrome and Graves disease achieved normal T4, but persistently elevated T3 on PTU and was therefore transitioned to once-daily methimazole (30 mg). However, while receiving methimazole, she developed a rash and was referred for I-131 therapy. Methimazole was discontinued and she was treated with propranolol monotherapy until she received I-131 therapy (4.3 mCi) approximately 1 month later. Notably, her T4 and T3 were 4 and 5 times the upper limits of the reference range, respectively, during the 1 month off anti-thyroid medications, but the propranolol reportedly provided adequate control of her hyperthyroid symptoms. Two days later, she presented with respiratory distress, tachypnea, fever, and hypertension consistent with thyroid storm and was treated with Lugol solution.

In 2001, Kadmon et al. published a case in which a 7.5-year-old boy with a 2.5 year history of poorly controlled Graves disease developed thyroid storm encephalopathy 13 days after methimazole withdrawal and 4 days after I-131 [6]. Notably, the patient developed hyperthermia, hypertension, heart murmur, and diarrhea 5 days after anti-thyroid medication withdrawal and 4 days before I-131 therapy. The patient went on to have a single tonic-clonic seizure and was diagnosed with thyroid storm 4 days after I-131 therapy. The authors concluded that his thyroid storm was a result of methimazole withdrawal and not I-131 therapy *per se*.

Our case documents the onset of thyroid storm within 24 hours of thyroid ablation and is therefore the earliest presentation of post-ablative thyroid storm in the pediatric literature. Given the details of the previously published cases noted above, it is possible that our patient developed thyroid storm due to her short course of pre-ablative PTU and PTU withdrawal, or a combination of PTU withdrawal and I-131 therapy. However, because her I-131 dosing, relative lack of pre-ablation signs or symptoms, severe and acute presentation occurred at about the same time, we suspect that our case represents true post-ablative thyroid storm.

At the time of this patient's treatment (2008), guidelines from the American Association of Clinical Endocrinologists (AAACE) stated that "elderly or cardiac patients with Graves disease may require anti-thyroid drug therapy before treatment with radioactive iodine, to deplete the thyroid gland of stored hormone

and reduce the risk of excessive post-treatment hyperthyroidism as a result of I-131-induced thyroiditis” [7]. However, at that time, many adult and pediatric endocrinologists offered, and still offer, definitive therapy with RAI at diagnosis in patients who were deemed to be “clinically stable.” While the clinical and biochemical description of a “clinically stable” Graves patient was previously open to interpretation, guidelines published in 2011 specifically recommend that children with free T4 levels greater than 5 ng/dL receive pretreatment with anti-thyroid drugs and beta blockade, and that ablation be delayed until T4 concentrations are normalized [8]. Notably, this recommendation was classified by the authors as “weak” and “low quality” based on “case series or unsystematic clinical observations.” As such, strong empiric evidence to support such a recommendation is lacking. Cases such as the one described herein, as well as the cases published by Hayek et al and Kadmon et al., provide further explanation for the recommendations emanating from experts faced with a dearth

of prospective data and charged with generating safe and effective consensus guidelines [6,8].

Conclusions

Although thyroid storm after thyroid ablation is rare, the significant morbidity and potential mortality of pediatric thyroid storm warrant further study to determine if children with markedly elevated thyroid hormone concentrations at diagnosis should receive prolonged pretreatment with anti-thyroid drugs. While such an approach may reduce the efficacy of I-131 ablation, it may also reduce and hopefully eliminate the risk of post-ablative thyroid storm.

Conflict of interest

The authors declare they have no conflicts of interest.

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