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Case Report

Two Cases of Thyroiditis in Adolescents Following COVID-19 Vaccinations

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Abstract

With the onset of the COVID-19 pandemic and the development of widespread vaccination strategies, there have been case reports in the adult literature suggesting an increase in thyroiditis after COVID-19 vaccination. We herein describe 2 children who presented with thyroiditis after COVID-19 vaccination. Two children who received Pfizer-BioNTech COVID-19 messenger RNA vaccines later developed symptoms of thyroid hyperactivity, had positive thyroid-stimulating immunoglobulin (TSI) levels and received treatment directed toward Graves disease. Our case series is the first to demonstrate Graves disease after COVID-19 vaccination in the pediatric population. Given this possibility, it is important for pediatricians to be watchful for symptoms of thyroiditis post vaccination to prevent treatment delays.

Key Words: Graves disease, COVID-19 vaccination

Abbreviations: HR, heart rate; mRNA, messenger RNA; T3, 3,5,3′-triiodothyronine; T4, thyroxine; TSH, thyrotropin; TSI, thyroid-stimulating immunoglobulin.

Introduction

Thyroid disease is estimated to occur in 1% to 2% of all children younger than 16 years [1]. With the onset of the COVID-19 pandemic in 2019, there have been case reports in the literature suggesting an increase in autoimmune endocrine diseases such as autoimmune hyperthyroidism both in children and adults [2]. Suggested pathogeneses include direct destruction from the virus itself, and/or indirect destruction due to an increase in proinflammatory cytokines [3–5]. With the development of widespread vaccination strategies, there have also been several case reports citing an increased incidence of autoimmune thyroiditis such as Graves disease post COVID-19 vaccination. All of these reports thus far have described adults [6–9]. At the time of submission, there have been no reports in the pediatric population.

The US Food and Drug Administration has approved 2 COVID-19 vaccinations for children aged 6 months through 18 years: Pfizer-BioNTech (Pfizer Inc) and Moderna (Moderna Inc). We hereby describe 2 children who presented with Graves disease after Pfizer-BioNTech COVID-19 messenger RNA (mRNA) vaccination.

Case Presentation

Case 1

Patient 1 is a 15-year-old previously healthy girl who initially presented to her pediatrician for evaluation of visual changes; she described seeing dark spots in her visual fields on standing. At this visit her vital signs were normal but blood work revealed a microcytic anemia with a low hemoglobin of 107 g/L (10.7 g/dL; reference range, 12.6-17.7 g/dL). Owing to the persistence of symptoms, blood work was repeated 3 months later. This showed resolution of anemia but incidentally revealed a suppressed thyrotropin (TSH) of less than 0.005 μIU/mL (reference range, 0.450-4.500 μIU/mL [mIU/L]) with an elevated free thyroxine (T4) of 33.1 pmol/L (2.57 ng/dL) (reference range, 0.93-1.6 ng/dL). The patient additionally noticed via her Apple watch that her resting heart rate (HR) had increased up to 130 bpm whereas previously it had been around 60 to 70 bpm. Her HR now rose above 200 bpm during exercise; this had never occurred in the past. She had received her first and second Pfizer-BioNTech COVID-19 vaccines 1 and 2 months before these laboratory values, respectively.

Diagnostic Assessment

When she presented to the pediatric endocrinology clinic 2 weeks after her initial blood work, her vital signs and physical exam were unremarkable, and she had a normal thyroid and eye exam. She continued to report transient elevations in HR while resting that became more persistent during activity as well as increased restlessness. She did not endorse any substantial past medical, surgical, or family history and denied taking any medications or supplements. Blood work at this visit confirmed a suppressed TSH of less than 0.005 μIU/mL (mIU/L) with an elevated total T3 of 3.4 nmol/L (223 ng/dL)

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Table 1. Laboratory values at time of diagnosis/initial visit

Laboratory values at time of diagnosis/ initial visit	Case 1	Case 2
TSH (0.450-4.500 µIU/mL [mIU/L])	< 0.005	< 0.005
Free T4 in pmol/L (0.93-1.6 ng/dL)	33.1(2.57)	39.1(3.04)
Total T3 in nmol/L(86–192 ng/dL)	3.14 (223)	5.9 (388)
Thyroid-stimulating immunoglobulin (0.00-0.55 IU/L)	3.59	5.43
Thyroid peroxidase antibody (0–26 IU/mL)	< 8	32
Thyroglobulin antibody (0.0-0.9 IU/mL)	< 1	37

Abbreviations: T3, 3,5,3′-triiodothyronine; T4, thyroxine; TSH, thyrotropin.

(reference range, 71-180 ng/dL) and total T4 of 164.7 nmol/L (12.8 µg/dL) (reference range, 4.5-12.0 µg/dL) (Table 1). She had an elevated thyroid-stimulating immunoglobulin (TSI) of 3.59 IU/L (reference range, 0.00-0.55 IU/L) and a T3:T4 ratio greater than 20. Thyroglobulin and thyroid peroxidase antibodies were found to be negative. Her symptoms and blood work were consistent with a diagnosis of thyroid hyperactivity.

Treatment

The patient was started on methimazole 5 mg 3 times per day (0.3 mg/kg/day). Six weeks later her total T4 and total T3 had improved to 7.6 µg/dL/dL and 1.31 nmol/L (85 ng/dL), respectively. Hence, her methimazole dose was reduced to 5 mg twice a day (0.21 mg/kg/d). Subsequent bloodwork every 4 weeks showed normalization of her thyroid function tests with decreasing TSI. She also no longer reported any symptoms and was not found to have any ocular findings of Graves disease.

Outcome and Follow-up

The patient was taken off methimazole 3 months after initiating treatment. Her most recent laboratory values at 5 months off the medication showed an undetectable TSI and reassuring TSH of 1.25 µIU/mL (mIU/L), T3 1.65 nmol/L (108 ng/dL), and T486.2 nmol/L (6.7 µg/dL).

Case 2

Patient 2 is a 14-year-old boy who presented to the emergency room with acute onset of extreme lower-extremity weakness on waking; he had collapsed on the floor trying to stand and walk to the bathroom. He had experienced a similar episode of lower-extremity weakness the week prior (also after waking from sleep) but had attributed it to exercise from the day before. That episode self-resolved and he did not seek medical care. He did not have any substantial medical or surgical history and was not taking any medications or supplements. His family history was remarkable for Graves disease diagnosed in his mother 8 months earlier. Notably, he received his first dose of the Pfizer-BioNTech COVID-19 vaccine approximately 1 month prior and his second dose just 2 days before this presentation. Aside from his weakness/paralysis, he denied any other complaints although he did mention mild cold-like symptoms a few weeks earlier that had resolved.

Diagnostic Assessment

In the emergency room his vital signs were notable for tachycardia to 120 bpm and hypertension to 140/61 mm Hg. Neurological exam was remarkable for decreased proximal muscle strength 1/5 bilaterally, absent deep-tendon reflexes, and an inability to raise his arms or flex at the elbows; his sensation was intact. His thyroid exam was normal and there were no notable eye changes. Laboratory evaluation showed a normal complete blood count and electrolytes except for a markedly decreased potassium level to 1.6 mmol/L (reference range, 3.5-5.1 mmol/L). He was diagnosed with hypokalemic periodic paralysis and received potassium supplementation that led to the resolution of his paralysis. His thyroid function tests revealed a markedly suppressed TSH of 0.007 µIU/L (reference range, 0.450-4.500 µIU/mL [mIU/L]) and an elevated free T4 of 48.1 pmol/L (3.74 ng/dL) (reference range, 0.93-1.6 ng/dL) (see Table 1). While awaiting a TSI level he was started on propranolol 20 mg 3 times a day and asked to follow up in the endocrine clinic.

Treatment

He was seen for an initial outpatient visit by endocrinology the following week; repeat thyroid tests showed a persistently suppressed TSH of less than 0.005 µIU/L (mIU/L), an elevated total T3 of 5.9 nmol/L (388 ng/dL) (reference range, 71-180 ng/dL), and an elevated free T4 of 39.1 pmol/L (3.04 ng/dL). He had negative thyroglobulin and thyroid peroxidase antibodies but had an elevated TSI of 5.43 IU/L (reference range, 0.00-0.55 IU/L), confirming Graves disease. Methimazole 10 mg 3 times a day (0.5 mg/kg/d) was initiated. This was switched to propylthiouracil after developing a rash concerning for an allergic reaction.

Outcome and Follow-up

The patient has since remained on propylthiouracil without further episodes of paralysis, and most recent laboratory values demonstrated persistent need for treatment: TSH less than 0.005 µIU/L (mIU/L), elevated free T4 of 32.2 pmol/L (2.5 ng/dL), elevated total T3 of 4.0 nmol/L (263 ng/dL), and TSI still 27.9 IU/L. A referral to ophthalmology was placed but not yet completed to assess for ocular findings of Graves disease.

Discussion

The Pfizer-BioNTech COVID-19 vaccine was first approved for children aged 16 years and older in December 2020. This was expanded to include children aged 12 to 15 years in May 2021, and then 6 years to 11 years in October 2021. More recently, on June 17, 2022, it was approved for children aged 6 months to 5 years. The most common side effects noted during the vaccine clinical trials were redness, swelling at the site of injection, fever, and irritability. But data on endocrinopathies post vaccination are sparse. To our knowledge, this is the first case series to demonstrate thyroiditis after Pfizer-BioNTech COVID-19 vaccination in the pediatric population.

All of the previous case reports describing new onset autoimmune thyroiditis such as Graves disease after COVID-19 vaccination have been in adults [6–9]. Singh and Howland [6] described 2 adult cases of Graves disease in the United States. Their first patient was a 42-year-old man who

developed hyperthyroid symptoms 2 days after receiving the Moderna booster vaccine. Their second patient was a 68-year-old woman who developed nonspecific symptoms within 24 to 48 hours after receiving the Johnson & Johnson vaccine and was eventually diagnosed with Graves disease a month later when she presented with atrial fibrillation. Both of these patients were started on methimazole and propranolol and neither was found to have eye findings. Vera-Lastra et al [7] reported 2 cases of Graves disease in health care workers that occurred after initial vaccination with the Pfizer-BioNTech COVID-19 vaccine; Graves disease occurred 2 and 3 days after vaccination. Both cases were found to have positive thyroid receptor antibodies and thyroid microsomal antibodies and were started on methimazole and propranolol. Another case report reported the incidence of Graves disease after the second dose of the Pfizer-BioNTech COVID-19 vaccine in a patient with a history of subclinical hypothyroidism [8]. Lastly, similar to the first patient in our series, Zettinig and Krebs [9] reported 2 cases of Graves disease in adults after the Pfizer-BioNTech vaccine who went into remission a few months after receiving treatment with thyrostatic medication.

The development of autoimmune diseases after vaccination has been well described in the literature. There have previously been case reports of thyroiditis following multiple vaccinations, including those for influenza, hepatitis B, and human papillomavirus. The correlation between human papillomavirus vaccination and subsequent thyroid disease seems to be the most well-described association [10].

Although the exact mechanism behind vaccination-induced autoimmune/inflammatory conditions is poorly understood, there have been 3 main hypotheses postulated thus far. The first hypothesis theorizes that the adjuvants in vaccines such as oils, lipopolysaccharides, mineral salts, and peptidoglycans induce immune reactions that can result in autoimmunity. This type of autoimmune disorder is called "autoimmune/autoinflammatory syndrome induced by adjuvants" (ASIA) and was first described by Shoenfield and Agmon-Levin [3]. The second hypothesis suggests molecular mimicry between COVID-19 viral proteins and human tissues, specifically the thyroid gland. This is supported by a study from Vojdani et al [4] that showed SARS-CoV-2 spike protein, nucleoprotein, and membrane protein all cross-react with thyroid peroxidase. This could theoretically lead to antibodies developed through vaccination against SARS-CoV-2 that may cause autoimmune thyroid conditions. The third hypothesis suggests an antigen-nonspecific mechanism in which an infection or vaccination leads to stimulation of innate immunity, which then leads to the activation of autoreactive T cells and the development of autoimmune thyroid conditions that may include Graves disease [4].

COVID-19 vaccines have been successful in reducing disease severity, spread, and complications. However, it is important for clinicians to be aware of possible adverse effects that may occur following vaccination including autoimmune endocrinopathies, even in the pediatric population.

There is little evidence of post–COVID-19 vaccination endocrinopathies in children. Our case series highlights the need for pediatricians to be watchful for symptoms of thyroiditis post COVID-19 vaccination to prevent treatment delays.

Learning Points

- Endocrinopathies can occur post COVID-19 vaccination in the pediatric population.
- Pediatricians need to be aware of the potential presentation of Graves disease after COVID-19 vaccination.
- Patients with thyroiditis after COVID-19 vaccination may go into remission within a few months after treatment.

Contributors

S.C. was responsible for concept and design, data acquisition, and drafting of the manuscript; C.F. helped with data acquisition and drafting of the manuscript; and E.O. and A.T. were involved in interpretation of data and critical review. All authors coordinated the care, read, and approved the final manuscript and are accountable for the work.

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Informed Patient Consent for Publication

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Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

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