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Thyrotoxic Periodic Paralysis in the Post-COVID Era: A Case Report with Literature Review

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ABSTRACT

Thyrotoxic Periodic Paralysis (TPP) is an acute potentially lethal emergency in patients with hyperthyroidism who present with sudden muscle weakness and hypokalemia. It is commonly precipitated by high carbohydrate or high salt content meals, strenuous exercise, stress, trauma, glucocorticoids, epinephrine, alcohol, or respiratory infections. COVID-19 infection or vaccination may represent a novel trigger for TPP. Furthermore, COVID-19 infection or vaccination may incite inflammatory processes leading to thyrotoxicosis, which can manifest as TPP. While COVID-19 causing subacute thyroiditis, euthyroid sick syndrome, Hashimoto's disease, or Graves' disease have been well documented in the literature; there have only been six case reports of post-COVID-19 TPP. Notably, all cases thus far have been restricted to male patients, and there is paucity of literature from North America. The purpose of this paper is to outline the first case of post-COVID-19 TPP in a female patient, who presented to the emergency department with acute paralysis and severe hypokalemia (2.2 mmol/L) three months after COVID-19 infection. Investigations in the emergency department showed thyrotoxicosis. She was treated with potassium replacement, which improved her paralysis. Subsequent investigations revealed severe hyperthyroidism from Graves' disease, which is currently managed with metoprolol and methimazole. Her hyperthyroidism improved without recurrent hypokalemia or paralysis. In addition, we outline the epidemiology, pathophysiology, precipitants, and management of TPP, with a particular focus on COVID-19 infection or vaccination precipitating TPP. We discuss post-COVID-19 TPP cases thus far described in the literature. Knowing that North American COVID-19 infection waves lagged Asia, we could anticipate additional future TPP cases.

Thyrotoxic Periodic Paralysis (TPP) represents an endocrine emergency characterized by sudden muscle weakness and low potassium [1–3]. While the weakness is usually rapidly reversible with potassium replacement, it can be distressing for patients and can cause cardiopulmonary collapse if untreated [1, 3]. The mechanism of TPP is complex and involves an intersection between genetic risk factors, thyrotoxicosis, and other precipitating factors that work together to cause intracellular potassium shift and impair skeletal muscle contractility [1, 2]. Common precipitants for TPP include high carbohydrate or high salt content meals, strenuous exercise, stress, trauma, glucocorticoids, epinephrine, alcohol, or even upper respiratory tract infections [1–3].

Coronavirus disease 2019 (COVID-19) is a pulmonary infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4, 5]. In addition to respiratory manifestations, COVID-19 can have a multitude of effects on the thyroid, which may be self-limiting, such as subacute thyroiditis or euthyroid sick syndrome, or permanent, such as Hashimoto's disease or Graves' disease [4, 6]. COVID-19 effects on the thyroid occur through a variety of postulated mechanisms including direct invasion of SARS-CoV-2 into thyroid tissue, post-infectious thyroid inflammation, or priming the immune system to infiltrate the thyroid gland in susceptible individuals [4, 6].

Interestingly, COVID-19 infection or even vaccination against COVID-19 may represent a novel trigger for TPP. First, COVID-19 can potentially worsen thyrotoxicosis in patients with pre-existing thyroid disease, precipitating TPP [4, 7]. Additionally, COVID-19 may initiate inflammatory cascades that can lead to the development of thyrotoxicosis in patients who are previously euthyroid, which subsequently manifests as TPP [5, 8–11]. While the effects of COVID-19 on the thyroid have been previously delineated in the literature, post-COVID-19 TPP represents a novel phenomenon with only six case reports that have been published worldwide [5, 7–11]. Notably, all cases thus far have been restricted to male patients, and no cases have been described in North America.

Here, we describe the case of a 34-year-old female with post-COVID-19 TPP who presented to the emergency department with acute paralysis and severe hypokalemia. On direct questioning, she endorsed thyrotoxicosis symptoms that began shortly after COVID-19 infection three months prior to her presentation.

Case Presentation

A 34-year-old Canadian female of Asian descent was brought to the emergency department (ED) by paramedics with acute-onset lower extremity weakness and tingling. Since her COVID-19 infection three months ago, she had tremor, anxiety, and 30-40 pounds of unintentional weight loss. These symptoms were attributed to residual COVID-19 effects, and she did not seek medical advice. Her COVID-19 infection was mild, managed at home without any hospital visits, and did not require any pharmacotherapy. She did not have any other symptoms, neck pain, or eye symptoms of thyroid disease. She was not on any exogenous iodine or thyroid hormone supplements. Her menstrual cycle was regular, and she was planning for pregnancy. She was working full time in a desk job and exercised regularly.

She was previously healthy. She had received a second dose of COVID-19 vaccine one year before her COVID-19 infection. Her only active medication was cetirizine for seasonal allergies. She had presented to a walk-in clinic three days before presentation at ED for a rash

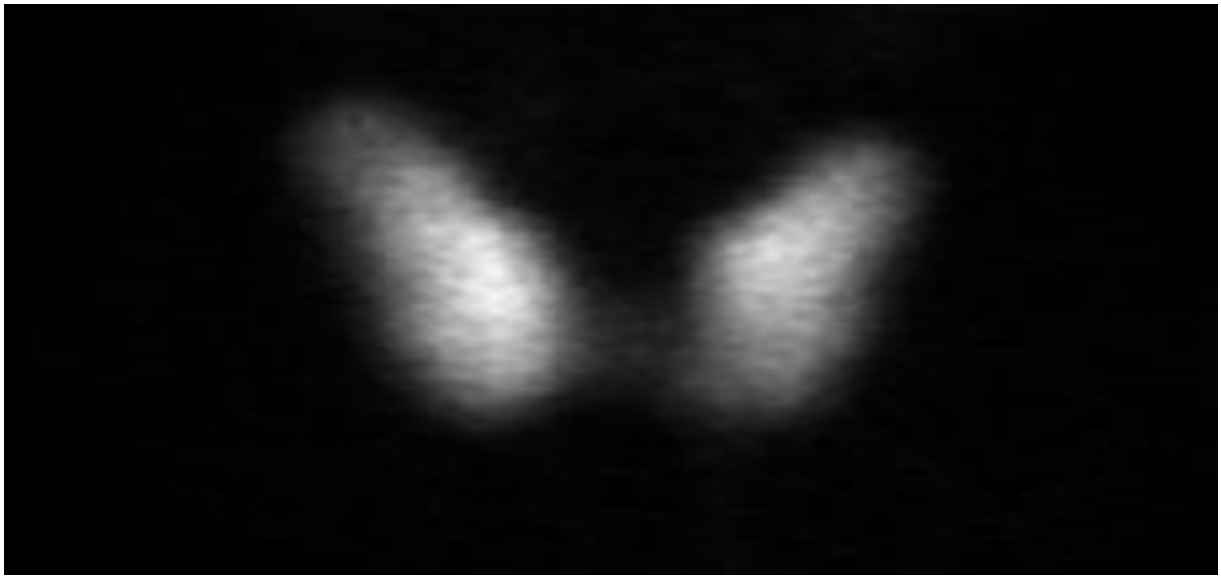
and was given intramuscular epinephrine and a three-day course of prednisone 50 mg daily for possible anaphylaxis. When seen in the ED, her rash had resolved. She ate a carbohydrate and salt rich meal the night before the presentation at ED. There was no family history of thyroid disease, hypokalemia, or paralysis. She smoked a few cigarettes per day for 16 years and used a few grams of marijuana recreationally for 16 years.

On physical examination at presentation, she had flaccid paralysis of bilateral lower limbs. Her temperature, blood pressure, respiratory rate, and oxygenation were normal, but she had high heart rate of 130 beats per minute. Focused examination revealed facial flushing, a slight hand tremor, and subtle right eyelid retraction without bulging of eyes. Her thyroid gland was bulky without any tenderness, palpable nodules, or bruits. Patellar reflexes were 1+ bilaterally.

Investigations in the ED were significant for severe hypokalemia with a potassium of 2.2 mmol/L. In the ED, her thyroid indices revealed an undetectable thyroid stimulating hormone (TSH) < 0.01 mIU/L (reference range 0.20-6.50 mIU/L), and subsequently, elevated free thyroxine (T4) 85.6 pmol/L (reference range 10-25 pmol/L), and free triiodothyronine (T3) 31.9 pmol/L (reference range 3-6.5 pmol/L). She was not aware of any diagnosis of Graves' disease. A serum pregnancy test ruled out pregnancy. Her creatine kinase, creatinine, and C-reactive protein were normal. Random blood glucose was 7.3 mmol/L. Electrocardiogram revealed prolonged PR interval (250 ms), flattened T waves, and normal QTc.

With high degree of clinical suspicion for Graves' disease, a serum TSH receptor antibody (TRAb) was drawn, which was positive at 7.33 IU/L (reference range < 1.75 IU/L). An outpatient Tc-99m pertechnetate scan revealed diffuse homogeneous uptake suggestive of Graves' disease (Figure 1).

Figure 1. Tc-99m pertechnetate scan of our patient demonstrating diffuse uptake suggesting Graves' disease.

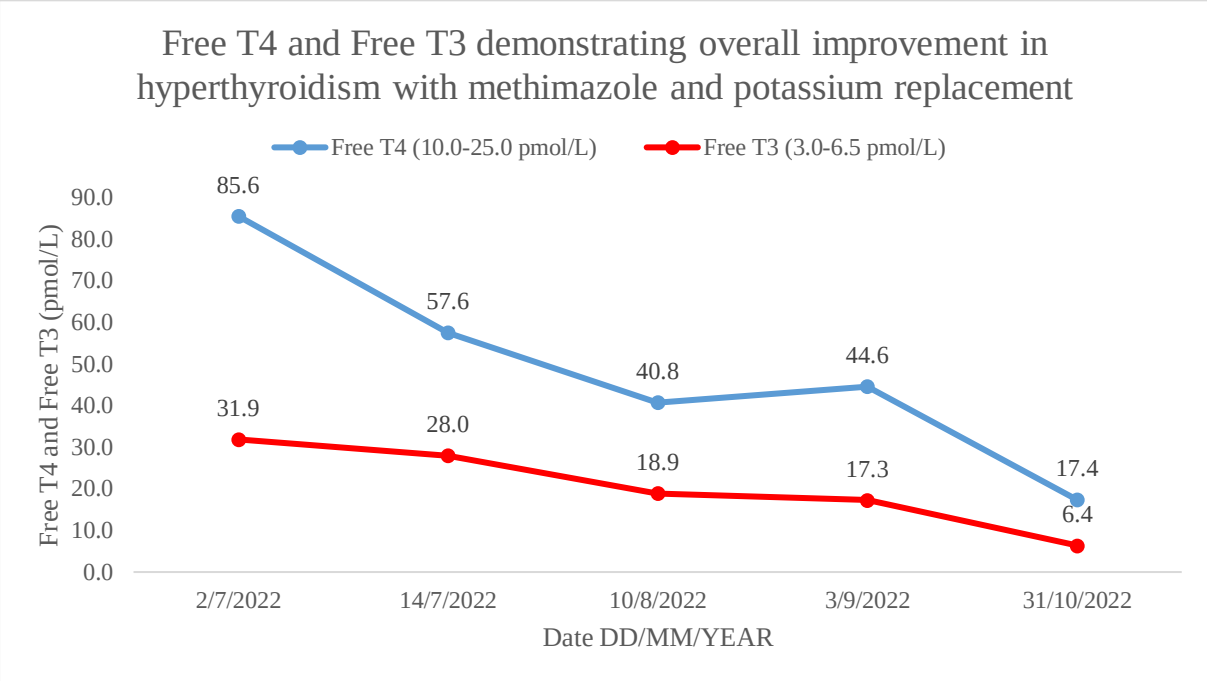


In the ED, her leg weakness improved after potassium replacement (30 mmol intravenous and 40 mmol oral). She was discharged home the next day on metoprolol 25 mg twice daily, methimazole 20 mg daily, as well as a two-week course of K-Dur 20 mmol daily. Follow-up investigations revealed improvement in hyperthyroidism (Table 1) with most recent thyroid indices showing TSH < 0.01 mIU/L, free T4 17.4 pmol/L, and free T3 6.4 pmol/L. She continued methimazole, metoprolol, and her potassium remained normal without

supplementation. She was advised to avoid triggers for thyrotoxic periodic paralysis and use effective contraception to defer pregnancy planning until her Graves' disease is well controlled.

Table 1. Thyroid function tests on presentation and follow-up investigations demonstrating overall improvement in hyperthyroidism after methimazole and potassium replacement therapy.

Thyroid function tests with reference ranges	2/7/2022	14/7/2022	10/8/2022	3/9/2022	31/10/2022
Potassium (3.6-5.2 mmol/L)	2.2 (L)		4.4	4.3	3.9
Thyroid Stimulating Hormone (TSH) (0.20-6.50 mIU/L)	<0.01 (L)	<0.01 (L)	<0.01 (L)	<0.01 (L)	< 0.01 (L)
Free T4 (10.0-25.0 pmol/L)	85.6 (H)	57.6 (H)	40.8 (H)	44.6 (H)	17.4
Free T3 (3.0-6.5 pmol/L)	31.9 (H)	28.0 (H)	18.9 (H)	17.3 (H)	6.4
TSH Receptor Antibodies (<1.75 IU/L)	7.33 (H)				



Discussion

Thyrotoxic periodic paralysis (TPP) is an uncommon manifestation of Graves' disease, occurring in 0.1-1.9% of patients [1, 2]. It occurs more commonly in people from Asia or Latin America with hyperthyroidism, with a typical age of 20-50 years [1, 2]. Despite hyperthyroidism occurring more commonly in women, TPP is more common in men with a male to female ratio of 17:1-70:1 [1–3]. Interestingly, there is diurnal and seasonal variation in TPP with most patients presenting at night between 2100h-0900h and during summer or fall [1–3].

While Graves' disease is the most common cause of thyrotoxicosis presenting as TPP, the underlying etiology of thyroid disease leading to TPP can include toxic adenoma, toxic multinodular goiter, subacute thyroiditis, amiodarone-induced thyroiditis, or TSH-producing adenoma [1, 2]. The pathophysiology of TPP is multifactorial, involving an intersection of genetics, thyrotoxicosis, and other precipitating factors [2]. Specific human leukocyte antigen (HLA) subtypes, mutations in potassium channels (Kir2.6), or mutations in calcium channels ($Ca_v1.1$) confer a higher risk for developing TPP [1, 2]. Thyroxine increases the number and activity of Na/K-ATPase channels in skeletal muscle through transcriptional and post-transcriptional mechanisms [1, 2]. Likewise, catecholamines and insulin can also increase Na/K-ATPase activity [1–3]. Given the multifactorial nature of TPP, the severity of thyrotoxicosis alone is not sufficient to predict TPP [1, 2].

With regards to precipitating factors for TPP, high carbohydrate or salt ingestion, strenuous exercise, stress, trauma, glucocorticoids, epinephrine, alcohol, or respiratory infections have been described [1–3]. Given the onset of thyrotoxicosis symptoms coinciding with COVID-19 infection in our patient, we hypothesize that the SARS-CoV-2 virus may have triggered an inflammatory cascade, ultimately culminating in Graves' disease. In addition, the patient ate a carbohydrate and salt rich meal the night before the presentation at ED. She had also received intramuscular epinephrine three days prior to her ED visit with TPP, followed by a three-day course of prednisone 50 mg for possible anaphylaxis. The increased adrenergic activity with epinephrine, hyperinsulinemia from prednisone, and background of undiagnosed post-COVID-19 Graves' disease all could have contributed to hypokalemia and subsequent paralysis in our patient.

COVID-19 infection or vaccination can manifest a variety of thyroid pathologies. First, in very sick patients, COVID-19 can cause euthyroid sick syndrome, which represents an adaptive response to physiologic stress with decreased thyroxine to triiodothyronine conversion [4]. Second, SARS-CoV-2 can cause subacute thyroiditis, which is associated with neck pain, usually transient, and self-resolving, although a small number of individuals require thyroid hormone replacement [4, 6]. Third, COVID-19 can trigger Graves' and Hashimoto's disease [4, 6]. The mechanism of COVID-19 causing thyroid disease is thought to be via direct invasion of SARS-CoV-2 into thyroid tissue, post-infectious thyroid inflammation, or by priming the immune system to infiltrate the thyroid glands of susceptible individuals [4, 6].

Rarely, COVID-19 infection or vaccination can precipitate TPP, and thus far, there have only been six case reports in the literature globally, as outlined in Table 2 [5, 7–11]. While the time from COVID-19 infection or vaccination to TPP seems to range from 0-22 days, one case report has described TPP occurring 90 days after COVID-19 infection [5]. The underlying etiology of thyroid disease leading to COVID-19-induced TPP is often Graves' disease or thyroiditis (subacute or painless) [7–9, 11]. Most patients require a combination of potassium replacement, β-blocker therapy, and anti-thyroid medication for the treatment of TPP and maintenance of euthyroidism [5, 8, 10]; one patient required a 6-week course of prednisolone for subacute thyroiditis [9] and another presented in extremis needing advanced cardiac life support for thyroid storm and pulseless ventricular tachycardia [7]. Of note, all reported cases thus far have been male patients; our case report is unique in that our patient is the first female with post-COVID-19 TPP. Our case also contributes to the literature in that it is the only other case where TPP manifested 90 days after the initial COVID-19 infection.

Table 2. Literature review demonstrating reported cases of thyrotoxic periodic paralysis following COVID-19 infection or vaccination and associated characteristics

Age/Sex (Reference)	COVID-19 infection or vaccination	Time from infection / vaccine to TPP (days)	Clinical presentation other than TPP	Potassium (mmol/L)	Investigations	Etiology of thyrotoxicosis	Treatment
42M (5)	Infection	90	Fever, cough	1.59	TSH < 0.005 µIU/ml fT4 3.75 ng/dl	NR	IV KCl Thiamazole 10
15M (7)	Infection	0	Palpitations, vomiting, diarrhea, fatigue, monomorphic VT	2.6	TSH < 0.01 µIU/ml fT4 4 ng/dl fT3 713 ng/dl	Graves' disease Thyroid storm	Hydrocortisone ACLS protocol
32M (8)	Infection	10	Weight loss, goiter, tremor	1.7	TSH < 0.004 mIU/L fT4 28.96 pmol/L TRAb 2.4 U/L	Graves' disease	IV KCl Propranolol 20mg Carbimazole 20mg
26M (9)	Vaccine: Moderna 2nd dose	22	Fever, headache, swollen thyroid, mild thyroid tenderness	1.8	TSH < 0.01 µIU/ml fT3 32.3 pg/mL fT4 > 7.77 ng/dL CRP 7.4 mg/dl TRAb/TPO neg Tg 667 ng/ml Tg-Ab 40 IU/ml	Subacute thyroiditis	Prednisolone 15mg x 6 weeks IV KCl
39M (10)	Vaccine: NR	6	-	3	TSH 0.008 µIU/ml fT4 2.49 ng/dl fT3 7.4 ng/dl TSI/TPO neg	NR	Methimazole Propranolol
33M (11)	Vaccine: Janssen	10	-	NR	TSH 0.012* fT4 37.39* TRAb/TPO neg Tg-Ab 203.3* CRP 5.16*	Painless thyroiditis	NR

ACLS Advanced cardiac life support, *CRP* C-reactive protein, *fT3* free triiodothyronine, *fT4* free thyroxine, *IV KCl* intravenous potassium chloride, *NR* not reported, *Tg* thyroglobulin, *Tg-Ab* anti-thyroglobulin antibody, *TPP* thyrotoxic periodic paralysis, *TRAb* TSH-receptor-antibody, *TSH* thyroid stimulating hormone, *TSI* thyroid stimulating immunoglobulin, *VT* ventricular tachycardia

*Units not reported

Management of TPP in the acute setting involves prompt potassium replacement to resolve paralysis [1–3]. Hypokalemia in TPP is due to intracellular potassium shifts rather than total body potassium deficit; overaggressive potassium replacement results in rebound hyperkalemia and cardiopulmonary complications [1–3]. Non-selective β-blockers have been suggested for patients with refractory hypokalemia, as they antagonize Na/K-ATPase pump activity and reduce intracellular potassium shift [1–3]. In the outpatient setting, β-blockers can be used for thyrotoxicosis symptoms and prevention of future paralysis [1, 2]. Definitive management of thyrotoxicosis is recommended in patients with TPP, which involves anti-thyroid medication, radioactive iodine, or thyroidectomy depending on the underlying etiology [1–3].

Ongoing close outpatient follow-up of our patient showed symptomatic improvement with no recurrence of weakness and normal potassium without any replacement. She has made significant dietary modifications by decreasing carbohydrate/salt consumption and has recently resumed regular exercise. Her thyroid indices are improving on methimazole (Table 1). Our team is discussing options for long-term management of Graves' disease, including definitive therapy, considering her wish to become pregnant soon.

Conclusion

In summary, TPP represents an endocrine emergency characterized by hypokalemia, thyrotoxicosis, and acute paralysis. Classical triggers include large carbohydrate/salt content meals, strenuous exercise,

stress, trauma, glucocorticoids, epinephrine, alcohol, or respiratory infections. COVID-19 infection or vaccination represents a novel under recognized trigger for TPP. COVID-19 infection may also initiate inflammatory cascades that cause Graves' disease, which subsequently can manifest as TPP. This is a unique phenomenon that has only been published in six case reports in the literature. Our report is the first one in the world presenting the case of a female patient with post-COVID-19 TPP. Treatment of TPP in the emergency setting involves potassium replacement and if needed β-blockers. β-blocker therapy with the restoration of euthyroidism in the outpatient setting is required to prevent recurrence. Physicians should be aware of the possibility of severe hyperthyroidism in patients who had COVID-19 infection or vaccination and have high index of clinical suspicion for TPP when relatively healthy young individuals present with weakness even if they do not have a known diagnosis of thyroid dysfunction.

Declarations

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