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CASE REPORT

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Recurrent, refractory hypokalemia as a diagnostic clue to thyrotoxic periodic paralysis in a patient with acute kidney injury and suspected Guillain-Barre syndrome

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Abstract

When clinical presentation is atypical, especially in a non-Asian population, the finding of recurrent and refractory hypokalemia can serve as a key diagnostic clue for timely diagnoses and management of thyrotoxic periodic paralysis. In suspected cases, complete thyroid laboratory panel should be measured so that T3 toxicosis is not missed.

KEYWORDS

refractory hypokalemia, diagnostic clue, thyrotoxic periodic paralysis, T3 toxicosis, Guillain-Barre syndrome, rhabdomyolysis, acute kidney injury, tenofovir nephrotoxicity

1 | INTRODUCTION

Hypokalemia can be multifactorial. When the primary driver of hypokalemia is obvious, it is easy to miss other contributing causes that could be vital to optimal patient management and outcomes. Our case report highlights the importance of recognizing recurrent, refractory hypokalemia as a diagnostic clue to thyrotoxic periodic paralysis.

Most cases of thyrotoxic periodic paralysis (TPP) have been reported in Asian men with the incidence of about 2% in thyrotoxic patients.[1] However, the incidence is reported to be only 0.1%–0.2% in non-Asian population.[2] A very high degree of clinical suspicion is therefore needed to diagnose thyrotoxic periodic paralysis in non-Asian population. We present a case of TPP in a 34-year-old Caucasian male who presented with clinical features suspicious of Guillain-Barre (GB) syndrome where the finding of severe, recurrent, and refractory hypokalemia served as a key diagnostic clue for timely diagnoses and management of TPP.

2 | CASE REPORT

Patient is a 34-year-old Caucasian male with a 5-year history of human immunodeficiency virus (HIV) infection, controlled on antiretroviral medications, who was admitted to the hospital for fever, nausea, and muscle weakness.

The patient was in his usual state of health until 8 days prior to this admission, when one morning patient began experiencing fever and nausea upon waking up that morning. Patient fell getting out of bed as his legs gave away from profound weakness in both legs which lasted for 15–20 min and improved but did not resolve until 3 h later. He fell once more that morning and developed pins and needle sensation in both legs since then. Five days later when he went to work, he had two more episodes of leg weakness with falls similar to the previous falls except for bilateral arm weakness. Patient has a 5-year history of HIV and was taking efavirenz, emtricitabine and tenofovir (Atripla) but had never been treated with a diuretic. Viral load had been undetectable on Atripla and

he was never diagnosed with an acquired immunodeficiency syndrome (AIDS) defining illness. On examination, thyroid gland was barely palpable without nodules. Heart rate was 64 beats/min, BP 153/74 mmHg, respiratory rate 16 breaths per minute, and oxygen saturation 96% on room air. Pupillary reflexes were normal with normal extraocular movements. Upper extremity strength was 3/5 proximally and 5/5 distally. He had weakness in both hip flexors 2/5, left worse than right, bilateral knee flexion and extension 3/5 but near normal strength 4/5 in both ankles. Bilateral knee reflexes were diminished. Rest of the physical examination was unremarkable. Patient had CKD with baseline creatinine 1.6 mg/dL and normal potassium levels prior. Initial laboratories on admission to the 1st hospital showed elevated WBC count of 16,000 per microliter, hypokalemia of 1.6 mEq/L, and elevated creatinine of 3.2 mg/dL. He had lumbar puncture and received single-dose vancomycin and ceftriazone. He was given IV fluids with 20 mEq potassium and transferred to the 2nd hospital for further workup and management. Electrocardiogram showed normal sinus rhythm. Bedside chest X ray, computerized tomography (CT) head without contrast, CT abdomen and pelvis, and magnetic resonance imaging (MRI) of thoracic and lumbar spine were unremarkable. Pertinent laboratories are summarized in Table 1.

3 | HOSPITAL COURSE

Because of initial suspicion of Guillain-Barre (GB) syndrome patient was started on intravenous immunoglobulin (IVIG). After 180 mEq of potassium replacement, potassium level was 1.8 mEq/L (Table 2). Because of recurrent, refractory hypokalemia in the absence of other identifiable triggers (discussed below), TPP was suspected and T3 toxicosis was found in the thyroid laboratory panel. Patient had significant improvement in muscle weakness and potassium levels after treatment with methimazole and propranolol in addition to ongoing potassium replacements (Table 2). Tenofovir was stopped. Patient was discharged on methimazole 20 mg twice daily and propranolol 40 mg every 6 h. Laboratories drawn 2 weeks after discharge showed elevated thyrotropin receptor antibody >40 IU/L (0–1.75) and thyroid stimulating immunoglobulin 3.9 (0–1.3 TSI index).

4 | DISCUSSION

Our patient did not have obvious symptoms of hyperthyroidism preceding the onset of muscle weakness. There is no correlation between severity of hyperthyroidism and TPP. In fact, approximately 50% of patients with TPP have been reported to have mild hyperthyroidism with no apparent symptoms.[3] In our case report, we recognize the presence of recurrent, refractory hypokalemia as a new diagnostic clue to TPP. AKI due to tenofovir nephrotoxicity was the primary driver of hypokalemia in our patient evidenced by transtubular potassium gradient (TTKG) of 9. However, with refractoriness to therapy based on the calculated potassium deficit, nonrenal etiology was suspected.

The intracellular compartment holds 98% of total potassium in the human body and only about 60 mmol of potassium fills the extracellular potassium pool.[4] The usual daily requirement is approximately 1 mEq per kilogram. Potassium deficit can be calculated by the formula: K deficit (in mEq) = (Knormal lower limit − Kmeasured) × kg body weight × 0.4. In our patient, if we consider the lowest potassium of 1.7 mEq/L and weight of 71 kg, potassium replacement dose in the 1st 24 h would be 121.4 mEq. Potassium level after 180 mEq of potassium replacement within 24 h in the 2nd hospital was 1.8 (additional 20 mEq was given in 1st hospital making the total to 200 mEq; see Table 2). The case had an absence of reported instigating factors associated with hypokalemia such as primary hyperaldosteronism, hypomagnesemia, hyperglycemia, vitamin B12 therapy, insulin therapy, bicarbonate therapy, and β2-adrenergic agonist therapy. Refractory hypokalemia presenting as muscle weakness would include TPP in the differential diagnosis. The patient's thyroid hormone levels were consistent with primary hyperthyroidism as the thyroid stimulating hormone (TSH) level was below the reference range and free triiodothyronine (fT3) level elevated. The T3 toxicosis likely led to TPP precipitating recurrent hypokalemia in the case. Notably patient's free thyroxine level was not elevated (Table 1).

Muscle weakness in TPP is a medical emergency and acute hypokalemia correlates with the severity of paralysis.[5] Thyroid hormones are known to increase the expression and activity of Na+/K+-ATPase.[4] It is estimated that if all the Na+/K+-ATPase pumps in the skeletal muscles are activated to their maximum potential, then the entire extracellular potassium pool (approximately 60 mmol) may be taken up into the muscle cells within 25 s.[6] Exercising muscles release potassium and cause vasodilation.[7] In TPP, the potassium is redistributed to intracellular compartment, predisposing to hypokalemia and rhabdomyolysis. In our patient, the T3 toxicosis lead to hyperactivity of Na+/K+-ATPase pumps leading to transcellular potassium shift, causing severe, recurrent, refractory acute hypokalemia. As expected with TPP, the patient did not respond to potassium replacements in excess of the calculated potassium deficit. Potassium levels eventually normalized with introduction of propranolol (a nonspecific beta blocker) and methimazole, an agent that inhibits the enzyme thyroperoxidase to decrease thyroid hormone synthesis.[8] Sympathetic adrenergic over activity in thyrotoxicosis enhances the activity of Na+/K+-ATPase leading to intracellular potassium shift. Propranolol suppresses the activity of Na+/

TABLE 1 Sequential laboratory data

Variable	Laboratory reference range	On presentation to 2nd hospital	10 h after admission	24 h after admission	35 h after admission	48 h after admission	84 h after admission
WBC (/uL)	3.31–10.31	12.55	10.21		8.95		8.59
Hemoglobin (g/dL)	14.2–18.2	13.4	12.6		11.8		12.2
MCV (fL)	83.8–96.6	87.1	86.9		85		86.8
Platelet (/uL)	140–370	428	428		387		376
Sodium (mEq/L)	136–146	144	145	145	146	143	143
Potassium (mEq/L)	3.5–5.1	2.3	1.7	1.8	2.8	3.7	3.4
Chloride (mEq/L)	103–112	111	112	110	111	110	113
Bicarbonate (mEq/L)	19–32	17	19	24	23	23	19
Glucose (mg/dL)	68–123		120	98	91	75	82
Creatinine (mg/dL)	0.5–1.3	2.8	2.8	2.2	2.2	1.8	1.5
BUN (mg/dL)	5–22	13	12	10	8	6	6
Calcium (mg/dL)	8.3–10.1	9.1	8.9	8.0	7.7	7.6	
Phosphorus (mg/dL)	2.5–4.5		1.4	1.6	2.1	1.6	2.4
Magnesium (mg/dL)	1.9–2.9	2.2	2.4				
Plasma osmolality (mOsm/kg)			301				
Albumin (g/dL)	3.5–5	3.9			2.9	2.9	
Total bilirubin (mg/dL)	0–1.3	0.7					
ALT (IU/L)	0–54	32					
AST (IU/L)	4–38	38					
Alkaline phosphatase (IU/L)	42–135	132					
Lactic acid (mmol/L)	0.5–1.99	0.7					
Creatine kinase (IU/L)	3–198	762	808		1059		12,685
Renin activity (ng/mL/h)	0.6–4.3				2		
Aldosterone (ng/dL)	4–21				<4		
TSH (mIU/L)	0.35–5.5			0.235			0.805
Free T4 (ng/dL)	0.89–1.76				0.56		0.62
Free T3 (pg/mL)	2.77–5.27				11		7.2
Vitamin B12 (pg/mL)	211–911				246		
Methylmalonic acid (0.40 μmol/L)	<0.4				1.85		
25-hydroxy Vitamin D (ng/mL)	30–100				<12.8		
Urine sodium (mEq/L)			28				
Urine potassium (mEq/L)			6.7				
Urine chloride (mEq/L)			<50				
Urine creatinine (mg/dL)			16				
Urine osmolality (mOsm/kg)			128				
Transtubular potassium gradient (TTKG)			9				
Potassium to creatinine ratio (mEq/g creatinine)			38.125				

Note: On Day 4, 24 h urine potassium was 77 mmol/day, 24 h urine protein 1043 mg/day with urine volume 3240 mL. CSF Studies: CSF clearly showed WBC 2/μL, RBC 1/μL, IG G index 0.58, albumin 27.8 mg/dL (reference range ≤27 mg/dL), CSF serology was negative for infectious etiology, IgM West Nile negative, CSF VDRL negative. CSF coccidioides Ig G and IgM antibody negative. CSF enteorvirus PCR negative, CSF IGG index 0.58 (reference level <0.85), CSF albumin 27.8 mg/dL (reference range <27 mg/dL). CSF culture was negative for growth in both the CSF taps. CSF cytology negative for malignancy. Serum/Plasma studies: Hepatitis A antibody positive, serology for hepatitis B and hepatitis C were negative. HIV viral load undetectable. PCR for serum sample was negative for CMV, gonococci, chlamydia. Serology for Lyme, Babesia, Ehrlichia and Anaplasma were negative. CD4 count was 441 cells/mm^3, serum cryptoccocal antigen negative. Renal biopsy: Renal biopsy showed acute tubular necrosis with no evidence of immune complex glomerulonephritis or focal segmental glomerulosclerosis. The necrotic debris did not stain for myoglobin. Electron microscopy showed well-preserved foot processes of visceral epithelial cells, glomerular basement membranes were slightly thickened, no electron dense deposit in mesangium. Tubular epithelial cells showed prominent vacuolization.

TABLE 2 Data on pharmacotherapy and response of potassium levels

Treatment	On admission to 2nd hospital	10 h after admission	24 h after admission	35 h after admission	48 h after admission	84 h after admission
Cumulative potassium replacement (mEq)[a] and corresponding		60	180	304.2	358.2	594.6
Serum potassium levels (mEq/L)	2.3→	1.7→	2.0→1.8	2.3→2.8	3.1→3.7	3.8→3.4→3.9→4.0→3.9
Cumulative phosphorus replacement (mmol)[b]			46		92	170
IV Calcium replacement					3 g	
Methimazole 20 mg PO Q8H cumulative				1 dose = 20 mg	2 doses = 40 mg	6 doses = 120 mg
Propranolol 40 mg PO 6 h				2 doses = 60 mg	4 doses = 160 mg	8 doses = 320 mg
IVIG 10% (25 g) cumulative		1 dose	2 doses		3 doses	3 doses
Vitamin B12 1000 mcg PO (cumulative)					1 dose	2 doses
Cholecalciferol PO (cumulative)				50,000 iu	51,000 iu	52,000 iu
Ceftriaxone IV 2 g Q24h (cumulative)	1 dose		2 doses			
Doxycycline 100 mg Q24h (cumulative)		1 dose		2 doses		

[a]Combined potassium replacement in the form of IV KCl. PO KCl, IV potassium phosphate (KPhos) and oral potassium phosphate-sodium phosphate (Neutra-Phos).

[b]Combined phosphorus replacement in the form of IV potassium phosphate (KPhos) and oral potassium phosphate-sodium phosphate (Neutra-Phos).

K+-ATPase thus preventing recurrent episodes of hypokalemia and paralysis.[9] In an isolated cause of TPP, there is no net potassium deficit as hypokalemia is attributed to intracellular potassium shift. Therefore, patients are often at risk of rebound hyperkalemia with potassium supplementation during the recovery of TPP.[10] Fortunately, our patient did not have rebound hyperkalemia, the risk of which was reduced due to superimposed renal potassium loss due to tenofovir nephrotoxicity.

5 | CONCLUSION

In many cases, hypokalemia can be multifactorial. When potassium replacements exceed the calculated deficit values by wide margin and with suboptimal correction of potassium, secondary causes should be entertained.

Persistent, refractory hypokalemia associated with muscle weakness should prompt suspicion for thyrotoxic periodic paralysis. In suspected cases, appropriate testing should include the measurement of free T3 levels along with a free thyroxine and TSH so that T3 toxicosis is not missed.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
VP: first and corresponding author, drafted the manuscript and responsible for acquisition of data, data interpretation and analysis. KC: coauthor, made substantial contributions to revision of the draft, data interpretation and analysis and to shape the manuscript. RC: Final author, supervised for critical revision of manuscript, data interpretation and analysis and shaping the manuscript. All authors approve the current version to be published and agree on the order in which the names are listed. All authors take accountability for all aspects of this work including accuracy and integrity.

ETHICAL APPROVAL
No patient identifiers were used in case report and patient permission was obtained to publish relevant clinical information.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author [VP].

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