Hypokalemic Periodic Paralysis and Spectrum of Thyroid Disorders: Analysis of 7 Cases from Northern India

Sir,

Hypokalemic periodic paralysis (HPP), a life-threatening complication of hyperthyroidism, is characterized by episodes of acute muscle weakness due to hypokalemia. Studies have reported incidence of 2% among Asians vs. 0.1–0.2% among non-Asians with hyperthyroidism.[1,2] The male to female ratio ranges from 17:1 to 76:1 among different ethnic groups.[2-4] Familial HPP and thyrotoxic periodic paralysis (TPP) are the most common cause of HPP among Caucasians and Asians, respectively.[5,6] The clinical manifestations are similar in both conditions. Hyperthyroidism may be clinically silent and patients may suffer recurrent attacks long before diagnosis.[3,7] Weakness is more common in lower limbs, with more severe proximal muscles involvement. Grave's disease (GD) is the most common cause of hyperthyroidism among patients with TPP, whereas other thyroid disorders have been implicated uncommonly. This case series highlights the presentation, precipitating factors, etiology of various thyroid disorders causing HPP, and the importance of early diagnosis and management in reducing morbidity and mortality.

This is a multi-center case series of 7 patients who presented with acute muscle weakness and hypokalemia at referral hospitals in New Delhi, Lucknow (UP), Gurugram (Haryana), and Amritsar (Punjab) in northern India. All of them were diagnosed to have thyroid disorders. Informed consent was obtained from all the patients. The baseline characteristics of all 7 patients are shown in Table 1. All were middle-aged Asian Indian men with more severe involvement of lower extremities. Three patients had multiple episodes of HPP, whereas 4 patients had only one episode at diagnosis. Out of the 3 patients with multiple episodes, 1 patient (patient 1) was on irregular treatment for GD for several years, and GD was diagnosed in 2 patients (patient 2 and 7) during second episode. Three patients presented in early morning hours.

For all patients, serum potassium was below 3 mmol/l with abnormal electrocardiogram (ECG). The trigger was identified in 3 patients. The bowel, bladder, and respiratory muscles were spared. The 99mTc thyroid scan was done in all patients except patient 4. All patients were diagnosed with thyroid disorders: 4 patients had GD, 1 patient toxic multinodular goiter (MNG), 1 patient painless thyroiditis, and 1 patient presented with primary hypothyroidism. Except patient 4 and 5, all other were treated with methimazole/carbimazole and propranolol [Table 2]. Six patients needed hospitalization.

TPP occurs commonly among Asian males in third to fifth decade of life.[2] Some studies have reported TPP among

Table 1: Baseline characteristics of patients presenting with HPP

Case	Age (years)	Sex	Weakness	Episodes of HPP	Signs/symptoms of thyrotoxicosis	Reflexes
1	36	M	LL>UL	3	Tremors, tachycardia	Absent
2	37	M	LL>UL	2	Weight loss, tremors	Absent
3	36	M	LL	1	None	Brisk
4	45	M	LL>UL	1	None	Delayed
5	38	M	LL>UL	1	Tremors, tachycardia	Absent
6	47	M	LL>UL	1	Sweating, tremors	Absent
7	38	M	LL>UL	2	Tremors	Absent

M=Male, LL=Lower limb, UL=Upper limb

Table 2: Biochemistry, imaging, diagnosis, and treatment of patients with HPP

Case	FT3	FT4	TSH	K+ (Pre/Post treatment)	Trigger	Thyroid Scan	Diagnosis	Treatment
1	9.63	2.77	<0.008	1.9/4.8	Alcohol	Diffuse Uptake	Grave's disease	Methimazole, β-blocker
2	7.42	2.14	<0.005	2.2/4.5	CHO rich food	Diffuse Uptake	Grave's disease	Methimazole, β-blocker
3	5.10	3.86	<0.001	2.4/5.1	None	Heterogenous uptake	Toxic MNG	Methimazole, β-blocker
4	1.23	0.56	57.6	1.5/3.9	None	Not done	Primary hypothyroidism	Levo-thyroxine
5	5.82	2.11	<0.005	1.9/4.8	None	Reduced uptake	Painless Thyroiditis	β-blocker
6	4.89	3.72	<0.01	2.1/4.1	None	Diffuse Uptake	Grave's disease	Carbimazole, β-blocker
7	6.31	1.95	<0.04	2.3/4.0	Alcohol	Diffuse Uptake	Grave's disease	Carbimazole, β-blocker

CHO=Carbohydrate, MNG=Multi-nodular goiter, Normal range: K+ 3.6-5.2 mmol/L, FT4 2.3-4.3 pg/ml, FT3 0.89-1.76 ng/dl, TSH 0.55-4.78 μIU/ml

Hispanics and Whites.[8,9] As TPP occurs commonly in males, androgens may have a role in pathogenesis. A Chinese study linked TPP episodes with elevated serum testosterone in men.[10] Higher muscle-to-body mass ratio because of testosterone leads to higher total amount of Na^+/K^+-ATPase in men, increasing their susceptibility.[11] In thyrotoxic patients with TPP, there is an increased number and activity of Na^+/K^+-ATPase pumps in skeletal muscle cell membranes compared to those without attacks, through both transcriptional and post-transcriptional mechanisms, leading to rapid and massive intracellular potassium shift.[12] The enhanced β-adrenergic response in thyrotoxicosis also increases Na^+/K^+-ATPase activity.

The triggers for attacks include carbohydrate or sodium rich meal, alcohol ingestion, strenuous exercise, trauma, emotional stress, infection, menses, cold exposure, etc.[13] These events may release epinephrine or insulin to cause intracellular potassium shift.[11] A lot of patients suffer from HPP without any trigger. We could identify trigger in only 3 (42.8%) patients in our study. Chang *et al.*[14] reported triggers in 34% patients, in a 10-year follow-up study of 135 patients. The most commonly identified triggers were high carbohydrate ingestion (12%), acute upper respiratory tract infections (URI) (8%), and strenuous exercise (7%).

The subtle symptoms of thyrotoxicosis may delay the diagnosis at initial presentation.[2,7] The symptoms of thyroid disorders were subtle in our patients and attacks preceded the diagnosis of thyroid disorder in 6 patients. Most cases of HPP have been attributed to GD in studies.[8,15] It may be because of the fact that GD is the most common cause of hyperthyroidism. Studies have reported association between HPP and other thyroid disorders such as painless thyroiditis, toxic MNG, toxic thyroid adenoma, and thyroid stimulating hormone (TSH) secreting pituitary adenoma.[11,15] Although association between HPP and primary hypothyroidism has been reported,[16,17] exact cause is not clear.

Our series suggests that hypokalemic paralysis can occur in the diverse setting of thyroid disorders. It is not a chance association, as normal potassium was maintained, without potassium replacement, only after the restoration of euthyroidism. If such observations are reported more in future, there may be merit in revising the term from "thyrotoxic periodic paralysis" (TPP) to "thyroid associated periodic paralysis" (TAPP).

The treatment of HPP includes immediate oral/intravenous potassium replacement therapy depending upon the severity of hypokalemia, along with non-specific β-blockers. Beta blockers cannot prevent attacks when given between attacks.[15,18] The main treatment of HPP involves control of hyperthyroidism using anti-thyroid drugs, radioiodine ablation or thyroidectomy, and the restoration of euthyroidism in other thyroid disorders. Precipitating factors must be avoided.

The hallmark of TPP is hypokalemia; serum potassium is usually less than 3.0 mmol/l. The degree of initial hypokalemia

has a direct correlation with the severity of attacks. Because of severe hypokalemia, our 6 patients needed hospitalization. Cardiac arrhythmias are common in TPP.[7] Typical changes of hypokalemia are seen in ECG such as atrial flutter/fibrillation, sinus tachycardia, atrial and ventricular ectopics, Paroxysmal supraventricular tachycardia (PSVT), and ventricular fibrillation. U waves and conduction defects have also been reported. ECG changes in our patients were consistent with those reported in hypokalemia. During acute attacks of TPP, immediate restoration of serum potassium through intravenous route is necessary along with oral propranolol. It results in more rapid response than oral supplementation.[19]

We conclude that quadriparesis due to TPP may be the first presentation of thyroid disorders. GD is the most common cause. Other thyroid disorders including primary hypothyroidism may also present as HPP. Because of the subtle signs and symptoms of thyroid disorders, diagnosis and treatment may be delayed. A thyroid function test should be done routinely while evaluating patients with hypokalemic paralysis.

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Conflicts of interest

There are no conflicts of interest.

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