Indian J Med Res 151, January 2020, pp 42-46
DOI: 10.4103/ijmr.IJMR_335_18

Quick Response Code:

Thyrotoxic periodic paralysis: A retrospective, observational study from India

Vishesh Verma[1], Yogesh Kumar[2], Narendra Kotwal[3], Vimal Upreti[3], K.V.S. Hari Kumar[3], Yashpal Singh[3] & Anil S. Menon[1]

[1]Department of Endocrinology, Command Hospital, Lucknow, Uttar Pradesh, [2]Department of Endocrinology, Command Hospital, Kolkata, West Bengal & [3]Department of Endocrinology, Army Hospital (R & R), New Delhi, India

Received February 15, 2018

***Background & objectives*: Thyrotoxic periodic paralysis (TPP) is an endocrine emergency presenting with acute-onset flaccid paralysis in a patient having thyrotoxicosis accompanied by hypokalaemia. This study was conducted to evaluate the clinical profile of patients with TPP presenting to three centres in India.**

***Methods*: This retrospective, observational study was conducted at three tertiary care Armed Forces medical centres, located at Lucknow, Kolkata and Delhi. The history, clinical features, treatment details and outcomes were evaluated.**

***Results*: Of the 244 patients with thyrotoxicosis, 15 were diagnosed with TPP and included in the study. These 15 patients (14 male and 1 female) had 32 episodes of TPP which were analyzed. The mean age was 30.2±6.2 yr (range: 21-39), and overt thyrotoxicosis was seen in all patients except one who had subclinical hyperthyroidism. Graves' disease was the most common cause of thyrotoxicosis (13/15) and the remaining two patients had subacute thyroiditis and gestational thyrotoxicosis. Hypokalaemia (serum potassium <3.5 mmol/l) was seen in 12 patients, and the mean serum potassium was 3.2±0.9 mmol/l (range: 2.1-4.9). All patients had flaccid weakness, predominantly involving the lower limb with no bulbar, respiratory or cranial nerve involvement. The average duration of paralysis was 10.6±5.7 h (range: 3-28 h).**

***Interpretation & conclusions*: Our study demonstrated an early age of presentation and presence of clinical and biochemical thyrotoxicosis in majority of patients with TPP. Hypokalaemia may not always be evident in patients with TPP.**

Key words Channelopathies - hypokalaemia - paralysis - periodic palsy - thyroid hormones - thyrotoxicosis - TPP

Thyrotoxic periodic paralysis (TPP) is an endocrine emergency presenting with acute-onset flaccid paralysis in a patient with thyrotoxicosis. This is often accompanied by hypokalaemia, and the attacks resolve on the treatment of thyrotoxicosis. TPP is the most common form of acquired periodic paralysis, and the disease is more common in the Asian ethnicity[1,2]. Early diagnosis and prompt treatment of TPP prevent

life-threatening complications of this curable disorder[1,3]. The disease has an atypical presentation and requires a high index of clinical suspicion for the diagnosis. TPP is a subcategory of patients presenting with hypokalaemic periodic paralysis (HPP)[4,5] and the diagnosis is difficult in patients without overt thyrotoxicosis and a fraction of patients are normokalemic[6].

Previous studies[7] have suggested that these patients are often misdiagnosed as idiopathic HPP (IHPP) or familial periodic paralysis (FPP). FPP is an autosomal dominant disorder due to a mutation in the gene coding for calcium channel on chromosome 1. Although hyperthyroidism is common in females, TPP has shown male preponderance in previous studies[3]. Kalita *et al*[8] have published a series of 52 patients with HPP, of whom TPP was seen in only nine patients. This study was conducted to review the clinical profile of patients with TPP presenting to three centres of the Armed Forces hospitals and identify the differences in these patients.

Material & Methods

This retrospective study was conducted at three tertiary care endocrine centres of Armed Forces located at Lucknow, Kolkata and New Delhi, India. All patients with a diagnosis of TPP presented to any of the three centres between January 2012 and June 2017 were included. Patient data were obtained by computerized hospital records, clinical notes and interview of patients attending the outpatient departments or admitted to the hospitals. A total of 244 (112 from New Delhi, 81 from Lucknow and 51 from Kolkata centres) thyrotoxicosis patients were evaluated, of whom only 15 (9 from New Delhi, 4 from Lucknow and 2 from Kolkata centres) patients had TPP, as shown in the Figure. Patients with incomplete clinical data and those using amiodarone or any other drugs that could affect the thyroid function, were excluded. The patients were divided into two groups, group 1 (TPP) and group 2 (thyrotoxicosis without TPP). The study protocol was approved by the Ethics Committee of the three centres.

Study measures: Details of history including any precipitating factors were noted from the available data and medical records. Clinical and systemic findings at the time of presentation were recorded. Thyroid function and biochemical parameters at the time of presentation were reviewed. The final diagnosis, treatment history and end outcome were also noted. All patients with clinical and biochemical thyrotoxicosis were managed as per the guidelines laid down by the American Thyroid Association/American Association of Clinical Endocrinologists[9,10].

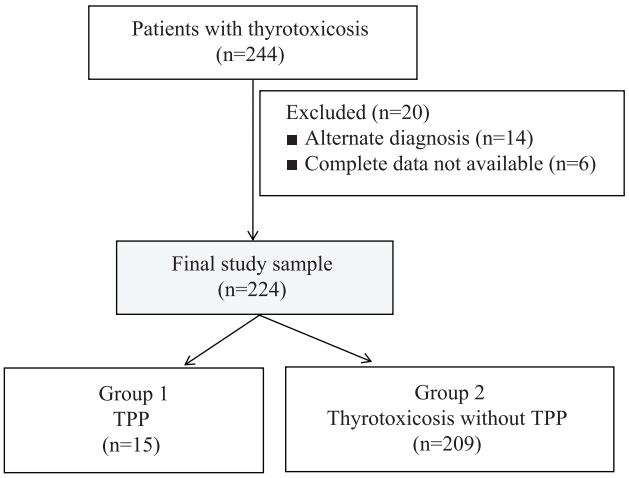

Figure. Flow diagram of the study. TPP, thyrotoxic periodic paralysis.

Study definitions: TPP was defined based on the presentation with acute flaccid paralysis, intermittent nature of the paralysis as manifested by spontaneous recovery or recovery with intervention, presence of thyrotoxicosis as per the biochemical criteria with elevated thyroid hormones and suppressed thyroid-stimulating hormone (TSH) and absence of other known causes of acute quadriparesis including myasthenia, Guillain-Barre syndrome, myelopathy, snakebite and botulism[3]. Graves' disease was diagnosed in the presence of clinical (hypermetabolic symptoms and eye signs), biochemical (elevated T3, T4 and suppressed TSH) and Technetium-99m pertechnetate scan (increased uptake) findings. Subacute thyroiditis (SAT) was diagnosed with similar clinical and biochemical findings of thyrotoxicosis along with reduced uptake in the Technetium-99m pertechnetate scan.

Statistical analysis: The continuous variables are presented as mean±SD and range and categorical variables using the frequency and percentages. The comparison between the two groups was done using the unpaired *t* test and Chi-square test. Data were analyzed using the Excel 2010 program (Microsoft®, Redmond, Washington, USA).

Results

The comparison of features between the patients with thyrotoxicosis with and without TPP is given in Table I. Briefly, patients without TPP (group 2) were older, had higher T4 (thyroxine) level and

the most common cause remained Graves' disease. The clinical and demographic data of the patients with TPP (group 1) are given in Table II. Briefly, precipitating factors could be identified in 24 (75%) of the 32 episodes, and majority had clinically overt thyrotoxicosis features and had Graves' disease as the aetiology for thyrotoxicosis. Overall, 32 attacks of TPP were observed with an average of 2.1±1.2 (range: 1-5) attacks per patient. The muscular weakness was variable, and none of the patients had bulbar, facial or ocular weakness. Myalgia preceded the attack of TPP in 14 (44%) of the 32 attacks. Myalgia was common in patients with exercise and carbohydrate meal (10 vs. 4) as precipitating factors, respectively.

Table I. Clinical comparison between the patients with and without thyrotoxic periodic paralysis

Feature	Group 1 (n=15)	Group 2 (n=209)
Age (yr)	30.2 (6.2)***	38.9 (9.3)
Sex (male:female)	14:1***	74:135
Graves' disease (n)	13	132
Subacute thyroiditis (n)	1	41
T4 (µg/dl), mean±SD	16.4±4**	20.5±5.2
Potassium (mmol/l), mean±SD	3.2±0.9***	4.2±0.8

P<0.01, ***<0.001 compared to group 2. T4, thyroxine

Table II. Characteristics of the patients with thyrotoxic periodic paralysis (TPP)

Parameter	Group 1 (n=15)
Age (yr), mean±SD	30.2±6.2
Gender	
Male (%)	14 (93)
Female (%)	1 (7)
Cause of TPP	
Graves' disease (%)	13 (86)
Subacute thyroiditis (%)	1 (7)
Gestational thyrotoxicosis (%)	1 (7)
Precipitating factor	
Exercise (%)	12 (80)
Heavy carbohydrate meal (%)	11 (73)
Fever (%)	1 (7)
Pattern of weakness (32 episodes)	
Paraparesis (%)	22 (69)
Quadriparesis (%)	8 (25)
Bulbar/respiratory (%)	Nil
Proximal (%)	24* (75)

*Data for other 8 episodes not available

Clinically, overt thyrotoxicosis was present in 14 patients and one had subclinical hyperthyroidism. Five patients were already diagnosed with thyrotoxicosis (Graves' disease) for a mean period of 8.4 months (range: 4-14 months) at the time of TPP. T4 was raised in 14 (93%) patients with a mean of 20.5±4.5 µg/dl (range: 11.1-30.2 µg/dl). Of the 32 episodes of paralysis, serum potassium reports were available for 17 (53%) episodes. The mean potassium levels were 3.2±0.9 mmol/l (range: 2.1-4.9 mmol/l. In three patients, hypokalaemia was not documented. Phosphorus levels were reduced in three patients. Of the 32 episodes, data for urine calcium/phosphorus ratio (UCPR) were available for only four episodes and the mean UCPR was 2.6±0.6 (range: 1.9-3.2). Alkaline phosphatase was raised in 13 (87%) patients with a mean of 222.7±66 IU/ml (range: 114-316 IU/ml). Two patients revealed a myopathic pattern during the attack on electromyography, which was resolved on correction of thyrotoxicosis.

The diagnosis of Graves' disease was confirmed in 13 (87%) patients and these were treated with antithyroid drugs and 11 amongst them were radio-ablated. The patient with SAT was managed with analgesics and the patient with gestational transient thyrotoxicosis was treated with oral propranolol. The average time to resolution of the periodic paralysis was 10.6±5.7 h (range: 3-28 h). It was also noted that spontaneous recovery took more time as compared to recovery with intervention (13.2 vs. 7.8 h; *P*=0.015). One patient with Graves' disease and post-ablative hypothyroidism had a relapse of TPP due to the overdosing of thyroxine replacement. None of the patients had a recurrent attack of TPP after the resolution of thyrotoxicosis during the mean follow up period of 15.4 (range: 2-48) months.

Discussion

The incidence of TPP in individuals of Asian descent is two per cent as compared to 0.8 per cent in non-Asian patients[11,12]. Our retrospective data showed 6.7 per cent patients with TPP in a group of patients collected at three centres. This could be due to the referral bias associated with the tertiary care centres, where only complicated cases of thyrotoxicosis are referred. TPP was shown to be predominantly affecting males in their second and third decades of life in all the case series[13]. The male-to-female ratio of TPP varies

amongst the countries with a reported ratio of 20:1 in Japan, 48:1 in the USA and 4 to 76:1 in China[12,14,15]. The predominance of males over females in our study could be explained by the natural profile of the disease being more common in the former[3] and the sample being derived from the armed forces population, where males outnumberd the females.

TPP is usually associated with proximal quadriparesis, and occasionally, patients are reported to have bulbar weakness and respiratory failure[8,13,16-18]. The weakness may be preceded by a prodrome of myalgias in less than half of the patients[19]. The attacks of HPP may be precipitated by high-carbohydrate meal, physical exertion, preceding febrile illness and often on getting up from sleep[20]. In our patients, heavy meal and strenuous exercise were the predominant risk factors. The daily routine in Armed Forces involves a high level of physical activity, which could be the precipitating factor. Chang *et al*[21] recorded precipitating factors in 34 per cent of their 135 patients. Our study documented a higher percentage (75%) of patients due to the targeted history taking and small sample. A quarter of patients with TPP may not have overt features of hyperthyroidism[11,22]. The occurrence of TPP does not depend on the severity of coexisting thyrotoxicosis, and thyroid hormone overdosage is rarely known to precipitate an attack of TPP in genetically predisposed individuals[3,4,23].

Hypokalaemia is a cardinal feature of TPP and is because of the inward movement of potassium ion across the cell membrane[11,24]. However, normal or increased potassium is not an uncommon finding in TPP[6,25]. Normalization of serum potassium precedes the recovery of muscle weakness[26]. Provocative tests to induce hypokalaemia with either insulin or carbohydrate challenge are often dangerous and unreliable and hence not recommended[3,27]. Serum phosphorus can be low and serum alkaline phosphatase (ALP) is raised in half of the patients with TPP, which may be utilized to differentiate TPP from IHPP. Electromyography (EMG) may show a myopathic pattern during an attack of TPP. EMG studies, muscle biopsy and CSF studies are occasionally required to either refute or corroborate the diagnosis of TPP[3]. TPP is often associated with hypercalciuria and hypophosphaturia. Therefore, spot UCPR (more than 1.7) has emerged as a tool for diagnosing TPP and to differentiate it from IHPP with a 100 per cent sensitivity and a 96 per cent specificity[1,2].

The treatment of HPP during an attack remains a careful potassium replacement (100-200 mEq) depending on the severity of weakness[13,28,29]. Potassium replacement decreases the time to recovery, and rebound hyperkalaemia is seen in about half of the treated attacks[30,31]. Regular potassium supplementation does not work as a prophylactic for the prevention of the TPP attack. Non-selective beta-blockers may be used to terminate an attack or for prophylaxis of recurrent attacks[13,28].

Our study was limited by the retrospective design and lack of complete data for all the TPP attacks. The data being derived from the Armed Forces hospitals may not be applicable for the general population.

To conclude, our study showed an early age of presentation of TPP precipitated by a heavy meal or strenuous exercise predominantly in males. The diagnosis is based on the demonstration of thyrotoxicosis and hypokalaemia during an attack of intermittent flaccid paresis. Hypokalaemia may not be mandatory in TPP, and further clinical studies involving a large sample size from India will delineate the role of new diagnostic aids such as spot UCPR.

***Financial support & sponsorship*:** None.

***Conflicts of Interest*:** None.

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For correspondence: Dr Yogesh Kumar, Department of Endocrinology, Command Hospital, Kolkata 700 027, West Bengal, India
e-mail: yogeshrewari77@gmail.com