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Impact of first-line treatment choice on long-term outcomes of hyperthyroid Graves' disease patients with thyrotoxic periodic paralysis

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ABSTRACT

Background: Thyrotoxic periodic paralysis (TPP) is a unique manifestation of Graves' disease. While it is uncommon in Asian, it is extremely rare in Caucasian patients (0.1–0.2%). Previous studies suggested that TPP indicate more severity of Graves' disease and definitive treatments should be used to prevent relapses.
Aim: To describe clinical features and impact of first-line treatment on long-term outcomes of TPP patients.
Method: A retrospective cohort study over 35 years (1985–2019) of TPP from Graves' disease patients was conducted. All cases were analyzed and their clinical courses were compared between those who received antithyroid drugs (ATD) versus radioactive iodine (RAI) as a primary treatment. None of them underwent surgery.
Results: A total of 2964 hyperthyroid Graves' disease patients were treated and followed-up at least 3 months over the study period. TPP was identified in 63 cases (2.1%) of all patients. There were 60 males and only 3 females with age at presentation of 35.0 ± 8.2 years. TPP was the first presentation of hyperthyroid Graves' disease in 82.5% of them. During the acute attack of TPP, all patients presented with bilateral lower limb flaccid weaknesses with median serum potassium of 2.1 mmol/L. No fatal TPP cases were found. RAI was selected as primary treatment in 27 patients (42.9%). Nearly all RAI-treated patients rendered hypothyroidism with the median RAI dose at 15 mCi. No patients who were in remission after RAI treatment developed recurrent attack of TPP. In the remaining 36 ATD-treated patients with mean follow-up time at 9.1 years, relapse was found in 10 patients (27.8%) after the drug discontinuation and 6 patients suffered recurrent TPP. Only 8 ATD-treated TPP patients (22.2%) went into remission.
Conclusions: TPP is a rare complication of hyperthyroid Graves' disease. Definitive treatment with RAI or thyroidectomy should be employed to prevent relapse and further attacks of TPP.

Introduction

Extrathyroidal manifestations of Graves' disease (GD) develop in minority of patients but could present as an initial presentation. Thyrotoxic periodic paralysis (TPP) is a unique manifestation of thyrotoxicosis which was described for almost a century [1]. While it is extremely rare in Caucasian patients (only 0.1–0.2% of patients with GD), but the incidence seemed to be rising in Western countries due to improved awareness and increased migration from of Asians [2–4]. In contrast, the prevalence of TPP in Asian population was on the decline (more than a 40% decrease in the incidence of TPP in Japanese patients from 1957 to 1991) [5]. Decreased in carbohydrate consumption and increased in potassium intakes among Japanese population were postulated for this observation [5].

Previous studies yielded conflicting results of TPP on GD severity [6–8]. The latest American Thyroid Association (ATA) guideline for management of hyperthyroidism recommended that definitive treatments should be used to prevent relapses [9]. However, high quality prospective studies are not available to support this recommendation. Even though high carbohydrate loads and strenuous exercise are both well-known precipitating factors of TPP, other less-known factors such as upper respiratory tract infection, glucocorticoid, alcohol have also been described [10]. Relapse of the paralytic attacks may develop if GD is not well controlled during treatment.

While radioiodine (RAI) treatment has been one of the preferred choices of treatment among physicians in the United States, antithyroid drugs (ATD) has been used as a primary treatment for Asian countries [11]. The long-term outcomes of ATD-treated hyperthyroid GD patients

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Table 1
Baseline characteristics of thyrotoxic periodic paralysis due to hyperthyroid Graves' disease in Thai patients (N = 63 cases).

	Total (N = 63 cases)	ATD (N = 36 cases)	RAI (N = 27 cases)	*P-value*
Male, n (%)	60 (95.2%)	34 (94.4%)	26 (96.3%)	0.733
Age at diagnosis (year)	35.0 ± 8.2	34.6 ± 8.3	35.5 ± 8.0	0.656
TPP at initial diagnosis, n (%)	52 (82.5%)	30 (83.3%)	22 (81.5%)	0.851
Duration of symptoms (month)	2 (IQR 1,24)	3 (IQR 1,16)	2 (IQR 1,18)	0.625
Family history of AITD, n (%)	26 (41.3%)	15 (41.7%)	11 (40.7%)	0.941
Precipitating factors, n (%)				0.266
- Unidentified	43 (68.3%)	22 (61.1%)	21 (77.8%)	
- Strenuous exercise	9 (14.3%)	6 (16.7%)	3 (11.1%)	
- Heavy meal	7 (11.1%)	4 (11.1%)	3 (11.1%)	
- Infection	4 (6.3%)	4 (11.1%)	0 (0.0%)	
Smoking, n (%)	12 (19.0%)	7 (19.4%)	5 (18.5%)	0.926
BMI before the onset of GD (kg/m^2)	25.5 + 4.1	24.9 + 4.1	26.3 + 4.1	0.278
BMI at initial presentation (kg/m^2)	24.1 ± 3.8	23.8 ± 3.7	24.4 ± 3.9	0.522
Weight status, n (%)				0.307
- Weight loss	49 (77.8%)	27 (75.0%)	22 (81.5%)	
- Neutral weight	11 (17.5%)	6 (16.7%)	5 (18.5)	
- Weight gain	3 (4.8%)	3 (8.3%)	0 (0.0%)	
Estimated thyroid size, n (%)				0.016
- Small (≤30 g)	50.8%	61.1%	37.0%	
- Medium (> 30–60 g)	36.5%	36.1%	15.9%	
- Large (≥60 g)	12.7%	2.8%	47.1%	
TSH (IU/mL)	0.009 ± 0.020	0.009 ± 0.020	0.010 ± 0.020	0.783
FT4 (ng/dL)	4.1 ± 2.4	3.7 ± 1.8	4.5 ± 3.0	0.325
T3 (ng/dl)	342.4 ± 106.7	349.4 ± 117.0	334.5 ± 97.1	0.699
Serum potassium (mmol/L)	2.1 (IQR 1.8,2.7)	2.1 (IQR 1.7,2.8)	2.0 (IQR 1.9,2.5)	0.829
Duration follow up (months)	103.2 ± 80.5	109.7 ± 81.9	94.6 ± 79.2	0.463

Abbreviation: AITD- Autoimmune thyroid disease; TPP – Thyrotoxic periodic paralysis.

with TPP would be valuable for clinicians to discuss the best choice of treatment with patients. In this study, we aim to study clinical features and long-term outcomes of different treatment modalities in a large cohort of Thai patients with hyperthyroid GD with TPP over three decades.

Materials and methods

This is a retrospective cohort study of Thai patients with TPP from hyperthyroid GD who were followed for at least 3 months at Theptarin Hospital, a tertiary endocrine center in Bangkok, Thailand between June 1985 and June 2019. Diagnosis of TPP included acute limb paralysis with complete recovery in 72 h with serum potassium concentration < 3.5 mmol/L. Other causes of periodic paralysis such as familial hypokalemic periodic paralysis, Gullain-Barre' syndrome, transverse myelitis, etc. were excluded. Details of TPP history, possible precipitating factors, and geographic residence were collected from the medical records. Thyroid function tests and plasma potassium concentration at the time of acute TPP attack were reviewed. The primary treatment modality for hyperthyroid GD and outcomes were analyzed.

Palpated thyroid size determined by treating physicians was transformed into thyroid volume on the basis of goiter size compared with normal thyroid size as follow: small (barely palpable or ≤30 g), medium (2–3 times when compared with normal thyroid gland), and huge (more than 3 times or ≥60 g). The presence of Graves' ophthalmopathy (GO) was defined as an inflammatory eye disease associated with GD and was classified by disease activity and severity as mild, moderate, or severe [11]. Serum T3, FT4, and TSH concentrations were measured by electrochemiluminescent immunoassays (Roche Diagnostics, Indianapolis, USA). The reference ranges of serum T3, FT4 and TSH were 60–177 ng/dL, 0.9–1.7 ng/dL, and 0.3–4.2 mIU/L, respectively.

For ATD-treated patients, our routine practice was to administer methimazole (MMI) for at least 12–18 months through titration method maintain euthyroid state. Remission of Graves' disease was defined as patients with normalized serum thyroid stimulating hormone (TSH) without ATD for at least 12 months [9]. If RAI was selected, a single fixed dose of RAI based on estimated thyroid size was prescribed. Our practice in using RAI treatment was to administer one dose of RAI aiming to resolution of hyperthyroidism (with or without the need for levothyroxine). Cure for hyperthyroidism after RAI was defined as euthyroid status for 6 months without any treatment or the need for levothyroxine replacement for post-treatment hypothyroidism. Final disease status was determined based on the last clinical visit during study period. This study was approved by the Institutional Review Board committee of Theptarin Hospital (EC No.4-2019).

Statistical analysis

Data was reported in mean with standard deviation, median with interquartile range, and number with percentage. Differences in the mean or median between groups were analyzed using a *t*-test and ANOVA test. Outcomes of TPP patients who were treated with ATD and RAI were compared using *t*-test for continuous data and Chi-square for categorical data. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS Statistical Package, version 20 (IBM Corp., Armonk, NY, USA).

Results

From 1985 to 2019, a total of 2964 adult Thai patients with hyperthyroid Graves' disease met the study criteria. Of those, 63 patients (2.1%) had TPP. Only 6 patients were admitted with paralytic paralysis in our hospital. The remaining patients had been initially treated at other hospitals. Of the 63 TPP patients, there were 60 males and only 3 females with the age at presentation of 35.0 ± 8.2 years. The mean duration of follow-up was 103.2 ± 80.5 months. Family history of thyroid disorders was found in 41.3%. No patient had family history of periodic paralysis. Most patients came from Bangkok and central region (84.1%) followed by Northeastern part of Thailand (9.5%). During the acute attack of TPP, all patients presented with bilateral lower limb flaccid weaknesses with median serum potassium of 2.1 mmol/L (IQR 1.8–2.7 mmol/L). The lowest serum potassium level was 1.4 mmol/L. No fatal TPP cases were found in our cohort. The baseline demographic

data and laboratory data were demonstrated in Table 1.

TPP was the first presentation of hyperthyroid Graves' disease in 82.5% of patients. In 23 patients with available data of timing of TPP attack, the onset of paralysis occurred in the late night or early morning in almost half of all episodes (47.8%). No seasonal variation was observed. Identifiable precipitating factors could be found in only 31.7% of patients with a carbohydrate-rich meal and/or strenuous exercise as leading cause (accounted for 80% of all identified factors). Among all TPP patients, ATD was the most preferred choice (57.1%), followed by RAI treatment (42.9%). No surgical treatment was done in our TPP cohort. The clinical characteristics and laboratory data between 2 groups was also revealed in Table 1.

During the mean follow-up time at 94.6 months, nearly all RAI-treated patients (85.2%) rendered hypothyroidism with the median RAI dose at 15 mCi. Only 3 RAI-treated TPP patients (8.3%) needed to continue MMI for the mean duration of 53 months. No patients who were in remission after RAI treatment developed recurrent attack of TPP. In the remaining 36 ATD-treated patients with the mean follow-up time at 109.7 months, only 8 of them (22.2%) went into remission. Relapsed Graves' disease was found in 10 patients (27.8%) and 6 patients suffered recurrent TPP attacks during the relapse period. The details of patients with recurrent TPP from ATD were summarized in Table 2.

Discussion

TPP is an uncommon complication of hyperthyroid GD which the control of hyperthyroidism is required to prevent the further attack of TPP. This study was the first and largest series of TPP patients in Southeast Asia over three decades. Our demographic data showed similar results with East Asian patients that male patients were predominant at the male to female ratio of 20:1 despite the higher incidence of GD in females [6–7,12]. Our as well as Singaporean study [13] did not confirm the observation from a study in Hong Kong [6] that summer season was the peak period for the incidence of TPP. Based on our long-term outcomes in both ATD and RAI-treated TPP patients, the definitive treatment with RAI or thyroidectomy should be employed to prevent further attacks of TPP. Remission rate from ATD as a primary treatment was only less than one-fourth of patients.

Even though TPP is one of the well-known emergencies in patients with thyrotoxicosis, the incidence is extremely low [14]. In the estimated incidence of admissions due to TPP in Hong Kong, the incidence was only 5.5 per million per year [6]. Hypokalemia is a cardinal feature of TPP despite increasing reported unusual cases with normal serum potassium levels [15,16]. Close monitoring of serum potassium during treatment with intravenous potassium replacement was recommended to avoid rebound hyperkalemia [17]. The severity of TPP correlates with the level of serum potassium, not the severity of thyrotoxicosis [10]. GD is still the most common cause of TPP; however, reported TPP cases were diverse [10]. A recent case report of Chinese patient with resistance to β-subunit of thyroid hormone (RTH) presented with TPP added to the list of cause of TPP and challenged the concept of RTH manifestations [18]. In GD patients with TPP, many reports showed that TPP was a sole initial presentation and other thyrotoxic symptoms and signs could be overlooked [13,19]. Our data were also in agreement with this observation as half of TPP patients revealed only small goiter size. Hypokalemic with paralysis is a heterogeneous syndrome which may results from TPP, hypokalemic periodic paralysis, or distal renal tubular acidosis (RTA). In Northeastern part of Thailand, distal RTA is one of the common major differential diagnosis from TPP [20,21]. It should be emphasized that various clinical clues (such as age of onset, gender, previous history of thyroid disease, etc.) might not be reliable to differentiate between the two conditions.

The fundamental abnormalities leading to TPP are complex and not completely understood yet. Hypokalemia due to a rapid shift of transcellular potassium has been postulated to be associated with increased sodium/potassium-adenosine triphosphatase (Na/K-ATPase) pump activity which may be stimulated by thyroid hormones, insulin and catecholamine [20]. The action of androgen on Na/K-ATPase pump activity was also explored as a possible explanation of TPP in strong male predominance [22]. Previous studies included Thai TPP participants revealed the potential role of insulin resistance as a key pathogenesis in TPP [23–25]. In 2010, a milestone discovery indicated that *KCN J18* gene mutations which alter the function of an inwardly rectifying potassium channel named Kir2.6 were detected up to 33% of patients [26]. However, there was heterogeneity of detected mutation rates between ethnicities (33.3% in Brazilian, 25.9% in Singaporeans and 1.2% in Hong Kong people). Previous studies that included Thai patients did not find this mutation in Thai participants but gene polymorphisms affecting the expression of *KCNJ2* gene (encoding Kir2.1) had been found in Thai TPP patients [27]. Since the landmark discovery of *KCNJ18* mutations in 2010, only 20 TPP cases with *KCNJ18* mutations have been reported worldwide [28]. Therefore, genetic variants that predispose to TPP remained elusive and genetic diagnosis for TPP could not be established simply based on *KCNJ18* gene mutation alone.

Although treatment of hyperthyroidism prevents recurrence of periodic paralysis, there have been no randomized controlled trials comparing different choices of treatment due to its rarity. In this study, our long-term results of ATD-treated patients are consistent with the overall low remission rate from other reports [9,29]. Recurrent TPP attacks during relapse period were found in 60% of ATD-treated patients with relapsed disease. Generally, the choice of treatment for hyperthyroid GD depends on patient's preference and local expertise but the key issue of TPP-associated GD is to ensure that TPP patients have minimal risk of subsequent relapse. Therefore, definitive treatment with RAI or surgical treatment should be employed to prevent further attacks of TPP [30]. Surgery is preferred in the treatment of Graves' disease in the cases with large goiter, moderate to severe GO, inability to tolerate RAI or ATD, or Graves' disease with suspicious nodule. In our present study, surgical treatment had been underused as a definitive treatment for hyperthyroidism from local practice preference among thyroidiologists [31]. However, this treatment option is still a viable option for patients who need to control their hyperthyroidism rapidly, patients who have huge goiters, or patients with suspected co-existing thyroid cancer [32].

There were several limitations which could have influenced our

Table 2
Clinical characteristics and time-course of ATD-treated TPP patients with recurrent TPP episodes (N = 6 cases).

No	Age(year)/Sex/estimated goiter size (gram)	Time to recurrence TPP (months)	Precipitating factor	Current status at the last follow-up	Duration of follow-up (months)
1	34/Male/60	16	Stress	ATD control	40
2	25/Male/40	55	Poor compliance	Remission	252
3	28/Male/20	29	Exercise	Post RAI hypothyroid	88
4	35/Male/15	104	URI	Post RAI hypothyroid	249
5	46/Male/35	88	Strenous exercise	Post RAI hypothyroid	150
6	32/Male/40	2	Strenous exercise	Post RAI hypothyroid	77

Abbreviation: ATD – Antithyroid drug; RAI – Radioactive iodine; URI – Upper respiratory tract infection.

results. First, the inherent weakness from the retrospective study should be acknowledged. There were many relevant missing data in medical records such as clinical and biochemical data at initial diagnosis of TPP, accuracy of GO assessment, clinical courses during TPP hospitalization, etc. Most of our TPP patients had been treated from other hospitals before attending our hospital. However, our present TPP series is one of the largest cohort studies with long-term outcomes in Asian patients. Our study can give insight into the clinical features and appropriate choice of treatment in TPP-associated hyperthyroid GD. Second, some important parameters especially serum level of TSH receptor antibody at the time of ATD withdrawal to predict the remission rate from ATD was missing. Third, the ultimate long-term outcomes from GD treatments included quality of life and mortality could not be assessed based on the design of retrospective study.

In conclusion, TPP is a rare complication of hyperthyroid Graves' disease in which definitive treatment with RAI or thyroidectomy should be employed to prevent further attacks. Remission rate from ATD as a primary treatment is low and recurrent TPP frequently occurred during relapse.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

CRediT authorship contribution statement

Krittadhee Karndumri: Conceptualization, Methodology, Formal analysis. **Yotsapon Thewjitcharoen:** Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Waralee Chatchomchuan:** Investigation. **Sriurai Porramatikul:** Investigation. **Sirinate Krittiyawong:** Investigation. **Ekgaluck Wanothayaroj:** Investigation. **Siriwan Butadej:** Investigation. **Soontaree Nakasatien:** Conceptualization, Methodology, Formal analysis. **Rajata Rajatanavin:** Supervision. **Thep Himathongkam:** Supervision.

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Authors' contributions

KK, YT, SB, and SN collected data, performed the statistical analyses, interpreted the data and drafted the manuscript. WC, SP, SK, EW, RR, and HT contributed to interpretation of the data and revised the manuscript critically before submission. RR and HT made substantial contributions to the discussion of results. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Ethical approval and consent to participant

This retrospective study is approved by the Ethics board committee of Theptarin Hospital (No.04/2019). No inform consent to participant was required as a retrospective study.

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