Thyrotoxic periodic paralysis in a Chinese population

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Summary

We retrospectively evaluated the characteristics of adult patients admitted with thyrotoxic hypokalaemic periodic paralysis in Hong Kong. From 1984 to 1993, 45 Chinese adult patients were admitted with acute limb weakness, plasma potassium $\leqslant 3.5$ mmol/l and thyrotoxicosis confirmed by laboratory investigations. All but one were male. Seventy-five percent of attacks occurred between 9pm and 9am. Half of the attacks occurred between July and October (49.1%), most commonly in August (20%). Mean ($\pm$SEM) plasma potassium on admission was 2.17 ± 0.08 mmol/l (range 1.1–3.5). In 15 episodes (27.3%), plasma potassium on recovery exceeded 5.0 mmol/l, while in three episodes (5.5%), potassium exceeded 6.0 mmol/l. No patient had a positive family history of thyrotoxic periodic paralysis. Only 28.9% had a known history of thyrotoxicosis before their first presentation with periodic paralysis. Twenty-seven (60%) had clinical evidence of thyrotoxicosis. Although all were biochemically thyrotoxic, 11.4% had only a mild degree of thyrotoxicosis (suppressed thyroid-stimulating hormone, high free thyroxine, but normal free triiodothyronine). One quarter of the patients had a normal erythrocyte zinc concentration, indicating either a short history of thyrotoxicosis or transient thyrotoxicosis. The diagnosis of thyrotoxic hypokalaemic paralysis should always be considered in Chinese patients with acute muscle weakness, especially in young males. Absence of clinical thyrotoxicosis does not exclude the diagnosis. Plasma potassium should be monitored carefully during treatment to prevent rebound hyperkalaemia.

Introduction

Periodic paralysis was first described in 1874 by Hartwig.[1] In Western countries, most cases of hypokalaemic paralysis are due to familial hypokalaemic periodic paralysis.[2] However, in Hong Kong, where 97% of the population are Chinese, the commonest cause is thyrotoxic periodic paralysis (TPP).[3] Association between thyrotoxicosis and periodic paralysis was first reported by Rosenfeld in 1902.[4] Mortality and significant morbidity associated with TPP, though uncommon, have been reported.[5-11]

We performed a retrospective study of adult patients admitted with hypokalaemic paralysis into a regional general hospital. We found that 45/56 patients (80.4%) were thyrotoxic. We describe the clinical characteristics of these 45 patients and review the findings with reference to previous publications.

Methods

Patients

Our data come from patients registered between 1984 and 1993. All were adults requiring emergency admission with varying degrees of limb weakness. At presentation, all had plasma potassium $\leqslant 3.5$ mmol/l. Their hospital notes were studied retrospectively. Only patients with unequivocal biochemical evidence of thyrotoxicosis are reported.

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Biochemical thyrotoxicosis was defined as total T4 > 140 nmol/l (normal 46–140) and/or free T4 > 21.8 pmol/l (normal 10.2–21.8) (before 1990) or thyroid-stimulating hormone (TSH) < 0.03 mIU/l (normal 0.3–4) and free T4 > 21.8 pmol/l (1990 or after).

Analytical methods

Thyroid-stimulating hormone was measured by the TSH double-antibody RIA test (Diagnostic Products) prior to November 1989, and subsequently by a sensitive immunometric assay (ICMA–TSH assay: Magic Lite, Ciba-Cornings). Total T4 (EMIT AGA thyroxine assay system, Syva) was used until November 1989, while free T3 (Amerlex-M free T3 RIA Kit: Amersham) and free T4 (two-step coated-tube RIA: Baxter Healthcare) became available in early 1988. The inter-assay coefficients of variation were < 12%. Erythrocyte zinc concentrations (RBCZn) were measured by atomic absorption spectrophotometry as described previously.[12] The coefficients of variation between assays were 5%. The normal range in our laboratory is 155–231 µmol/l red cells.

Thyroid anti-thyroglobulin and anti-microsomal antibodies were measured by passive haemagglutination using Thymune-M and Thymune-T kits (Wellcome Reagents). Titers ≥ 1 : 20 and 1 : 400, respectively, were considered positive.

Statistical analysis

All data were expressed as means ± SEM. Correlation between plasma potassium level on admission, thyroid function test and other clinical parameters were tested by Spearman's least square analysis with $p < 0.05$ as significant.

Results

There were 78 admissions due to hypokalaemic paralysis. Detailed and accurate information was obtained in relation to 73 of these (93.6%), and 55 were judged due to TPP (75.3%). Fifty-six patients accounted for the 73 admissions (some had more than one admission), of whom 45 were diagnosed as TPP (80.4%). Thus 45 TPP patients had 55 admissions. Six patients (13.3%) were admitted twice, while two patients (4.4%) had three admissions.

The Prince of Wales Hospital provides a service to the New Territories East district of Hong Kong with a population of approximately 1 million in 1992. Thus the approximate incidence of TPP in Hong Kong is estimated to be 4.5 patients per million per year.

Of the 45 patients, 44 were male and one was

female. All were ethnic Chinese. The mean age was 33.4 ± 1.0 years (range 22–55). In most patients, the onset of paralysis occurred either late in the evening or early in the morning. Seventy-five percent of attacks developed between 9pm and 9am, with two peaks, one at 9pm to 12 midnight (26.9%) and another at 3am to 9am (32.7%). Attacks occurred most commonly in August (20%), and 49% occurred between July and October during the hottest time of year in Hong Kong.

We have graded the severity of paralysis into three categories: mild weakness, whereby patients could still walk without assistance; moderate weakness, whereby assistance to walk was needed; and total paralysis. Most TPP patients (74.6%) were admitted with total paralysis. Only 1.8% were admitted with mild weakness and 23.6% with moderate weakness.

Plasma potassium concentrations on admission ranged from 1.1 to 3.5 mmol/l (mean 2.17 ± 0.08) (Figure 1). Intravenous potassium requirements prior to recovery ranged from zero to 230 mmol (mean 73.2 ± 7.5). A few received oral potassium supplements only (26.8–162.0 mmol, mean 103.2 ± 5.6). Upon recovery, peak plasma potassium concentrations ranged from 3.6 to 7.2 mmol/l (mean 4.7 ± 0.12) (Table 1). In 15 cases (27.3%), potassium on recovery transiently exceeded 5 mmol/l, while in three (5.5%), 6 mmol/l was exceeded.

Exercise and high carbohydrate loads are well-known precipitating factors for TPP. 7.3% of our patients had exercise followed by rest before the onset of paralysis. Heavy meals or sweet snacks were recognized as precipitating factors in 23.6%.

No patient had a positive family history of TPP, although seven patients (17.8%) had a family history of thyrotoxicosis in one or more family members. Twenty-nine (64.4%) gave a prior history of thyrotoxic symptoms before TPP attacks and 27 (60%) were clinically thyrotoxic at presentation. Goiter was present in 27 but none had significant infiltrative ophthalmopathy. Two (4.4%) had previously undergone partial thyroidectomy (3 and 13 years before TPP attacks) and in both, relapse of thyrotoxicosis occurred before their paralytic attacks.

The results of thyroid function tests were as

Table 1 Highest potassium concentrations on recovery

Highest potassium concentration on recovery (mmol/l)	Number of admission	Cumulative percentage
> 7.0	1	1.8
6.0–7.0	2	5.5
5.6–6.0	0	5.5
5.1–5.5	12	27.3
≤ 5.0	40	100.0
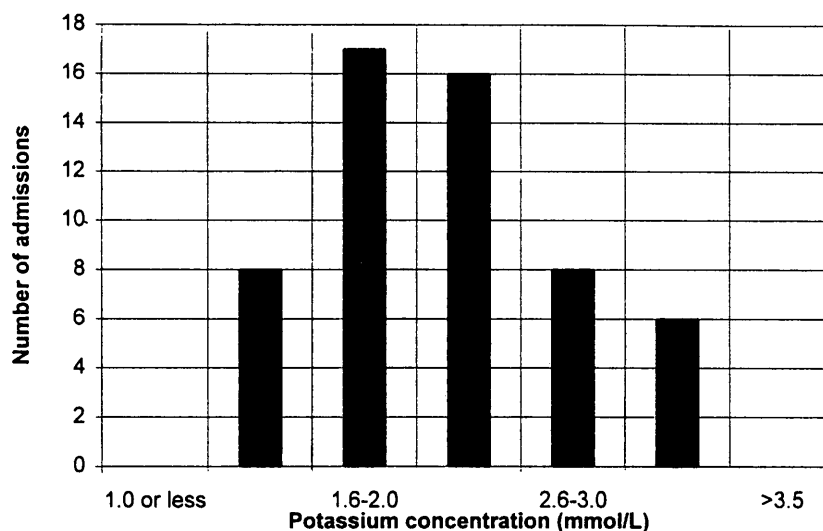
Figure 1. Potassium concentrations on admission.

follows: for those who were diagnosed to be thyrotoxic before 1990, all had total T4>140 nmol/l and/or free T4>21.8 pmol/l. For those who were diagnosed to be thyrotoxic after 1990, all had TSH <0.03 mIU/l and free T4>21.8 pmol/l. In most patients (88.6%) free T3 exceeded 8.2 pmol/l (normal 3.3–8.2). RBC Zn was <155 μmol/l red cells (normal 155–237) in 75% of those in whom it was measured (n=26). Positive thyroid anti-microsomal and/or anti-thyroglobulin antibodies were recorded in 66% of patients.

Of the 55 admissions, eight (14.6%) were incorrectly diagnosed at presentation. Misdiagnoses included Guillain-Barré syndrome, acute spinal cord compression, myelitis and hysteria.

Discussion

Epidemiology and clinical presentation

The incidence of TPP in the West is uncertain. Our data from Hong Kong indicate an incidence of approximately 4.5 patients per million per year. The figure is almost certainly an underestimate, because individuals with mild attacks may not require admission and those with normokalaemia have been excluded from this analysis. Our incidence of admissions due to TPP is 5.5 per million per year.

TPP is known to occur predominantly among Asians, although it has also been reported in Hispanics,[13] Blacks[14] and American Indians.[15] Figures from the Mayo clinic indicate that TPP occurs in 0.1 to 0.2% of non-Asian thyrotoxic patients[16] compared to Japan where the percentage ranges from 1.9 to 8.8%.[17,18] Among Chinese thyrotoxic patients, the figure was 1.8% in 1967.[3]

Previous reports indicated that the patients are

usually 20 to 40 years old.[3,19] Our patients lie within the age range 22–55, with a mean of 33.4. This coincides with the usual age distribution for thyrotoxicosis.

Male predominance of TPP is well recognized. Male to female ratios vary from 17:1 to 20:1 in Japan,[18,20] 33:1 to 48:1 in USA[21] and 76:1 in Southern China.[3] Our figure is 44:1. This male predominance may reflect the action of androgens on Na,K-ATPase activity.

High carbohydrate loads and strenuous exercise are well-recognized precipitating factors for TPP.[22] TPP does not occur during exercise but during the period of rest that follows exercise.[3,22] Other possible precipitating factors include trauma, cold exposure, infection, menstruation and emotional stress.

In Hong Kong, attacks are most common during August (20%) and about half occur between July and October (49.1%). This coincides with the hot season and is consistent with a previous report.[3] Increased consumption of sweet drinks, outdoor activities and exercise, and increased potassium loss in sweat are possible factors explaining the seasonal pattern. However, as a subtropical city, Hong Kong does not have very low temperatures during winter and TPP attacks are not that uncommon even in winter. In tropical cities such as Singapore, seasonal variation is not seen.[23,24]

TPP usually occurs in the late evening or early morning.[3] Our study confirms this, and shows that most attacks (74.5%) occur between 9pm to 9am. This agrees with data from Singapore, 88.5% of 51 attacks occurring between 6pm and 8am.[23,24] There are two peaks, at 3am to 9am (40.0%) and 9pm to 12 midnight (21.8%), respectively. The evening peak would correspond to the period of rest following evening exercise and dinner. The peak in the early

hours of the morning probably reflects insidious onset of paralysis during the early hours of sleep.

Thyroid function

Early reported figures for clinical manifestations of thyrotoxicosis in TPP vary from 73 to 100%.[3,20,25] Recent reports emphasize the subtlety of thyrotoxic symptoms and signs in many patients with TPP.[16] In our experience, 29% have known thyrotoxicosis prior to TPP, 64% have thyrotoxic symptoms and 60% are clinically thyrotoxic at presentation. Although these figures come from retrospective analysis of case reports which may not be totally reliable, they do indicate that a significant proportion of patients are clinically euthyroid despite subsequent biochemical confirmation of thyrotoxicosis.

TPP attacks occur only when thyrotoxicosis is present. Attacks can be induced by insulin and carbohydrate administration in hyperthyroid patients with a history of TPP, but not in TPP patients who have become euthyroid.[3] Paralytic attacks can recur with relapse into a thyrotoxic state,[23] and can be induced by exogenous thyroid hormone.[17] In our study, two patients had been in remission after partial thyroidectomy for 3 and 13 years, respectively. TPP attacks recurred only in association with thyrotoxic relapse.

The underlying cause of thyrotoxicosis or hyperthyroidism appears not to influence the presence or absence of TPP. Attacks have been reported in association with Graves' disease, toxic nodular goiter,[26] solitary toxic thyroid adenoma,[16] the Jod-Basedow phenomenon,[21] lymphocytic thyroiditis,[19] and administration of exogenous thyroid hormone.[27] In our study, Graves' disease was by far the commonest cause, and this reflects the pattern of thyroid disease in the Hong Kong community.

The severity of hyperthyroidism correlates poorly with TPP attacks. There are recent reports showing that the hyperthyroidism is 'clinically silent' in some cases.[16] In our study, more than one-tenth (11.4%) had relatively mild thyrotoxicosis (suppressed thyroid-stimulating hormone, high free thyroxine but normal free triiodothyronine).[28] Interestingly, 25% of our patients had normal RBC Zn. We have previously reported that RBC Zn concentration reflects the integrated functional state of the thyroid over the preceding 2 to 3 months in a manner similar to glycosylated haemoglobin in diabetic patients.[29] This has been confirmed by other studies.[30,31] The normal RBC Zn in 25% of our patients therefore signifies recent onset of thyrotoxicosis. Thus TPP may be an early manifestation of thyrotoxicosis, the severity of the symptom leading to earlier diagnosis in vulnerable patients.

Pathophysiology

HLA markers have been extensively studied. HLA A2, Bw22, Aw19 and B17 have been reported to be more common in TPP patients in Singapore and Thailand.[23,24,32] In Caucasians, the disease is associated with HLA DR3.[33] In our population, the prevalence of Bw46 has been reported to be increased in patients with TPP.[34] We also found a weak association of HLA B46, DR9 and DQB1*0303 in Hong Kong Chinese males with TPP.[35]

Thyroid hormone can increase Na,K-ATPase activity in skeletal muscle, liver and kidney[36,37] and induce influx of plasma potassium into the intracellular space. Thyrotoxic patients, both with or without TPP, have significantly greater lymphocyte and platelet sodium pump activity than normal.[38,39] Furthermore, our untreated thyrotoxic patients with TPP have higher platelet Na,K-ATPase activity and *in vivo* sodium pump activity compared to other, equally thyrotoxic, subjects without TPP.[39] Both thyrotoxic groups have higher activity than normal subjects. When thyrotoxicosis is corrected, the Na,K-ATPase activity in TPP patients is restored to values indistinguishable from those in healthy subjects. It would thus appear that thyroid hormone increases Na,K-ATPase in a reversible manner and that this enhancement is exaggerated in TPP subjects, suggesting an underlying predisposition. Thyrotoxicosis, therefore, may precipitate TPP only in susceptible individuals. This difference in susceptibility could be genetic in nature, either directly or indirectly. TPP subjects may have a qualitative and/or quantitative change in Na,K-ATPase activity which renders them more sensitive to the stimulating effect of thyroid hormones. A recent report localizes a hypokalaemic periodic paralysis locus to chromosome 1q31-32 in several Caucasian families of different geographic origin.[40] Familial/sporadic hypokalaemic paralysis is almost identical to TPP except for the absence of thyrotoxicosis. It remains to be seen whether similar findings may be obtained in TPP subjects and whether TPP is an 'intermediate' form of familial hypokalaemic paralysis, which is only unmasked by a thyrotoxic state.

Treatment

Numerous drugs have been used in attempts to prevent TPP. Reserpine may alleviate most sympathetic manifestations of thyrotoxicosis, but fails to prevent TPP.[41] Acetazolamide has been studied in patients with hypokalaemic periodic paralysis and has been claimed to be the most effective agent in preventing paralytic episodes.[42] However, it is inconclusive in TPP, both success and failure having been reported with acetazolamide as a prophylactic

agent.[43,44] The most successful drug is propranolol. Young *et al.* reported a 71% success rate with propranolol in achieving partial or complete protection from high-carbohydrate-diet-induced paralysis in thyrotoxic patients with history of TPP.[44] Conway *et al.*, in a smaller study, reported similar findings that beta-adrenergic blockade in prevented paralytic episodes in TPP.[15]

TPP attacks occur only when patients are thyrotoxic. Thus aggressive treatment of the thyrotoxicosis is indicated. Some have recommended radioactive iodine for the treatment of all cases.[45,46] However, others consider surgery the best form of definitive therapy, especially for toxic nodules or toxic multinodular goiter.[47] The choice may depend on local expertise and cultural factors, but the key issue is to ensure that TPP patients have minimal risk of subsequent relapse. Our current practice is to use propranolol and propylthiouracil to establish rapid control of the thyrotoxicosis, followed by ablative radioactive iodine therapy in the majority of cases.

Conclusions

Hypokalaemic paralysis is not uncommon in Hong Kong, the most important cause being TPP, which accounts for 80% of cases. TPP is one of the commonest presenting feature of thyrotoxicosis in Chinese males. The diagnosis should always be considered when dealing with patients with acute muscle weakness especially if they are young and male, with severe paralysis, a history of recurrent similar attacks with quick recovery and if the attacks are acute in onset. Absence of clinical or previous evidence of thyrotoxicosis does not exclude the diagnosis. In treating TPP with intravenous potassium, close monitoring of plasma potassium is essential to prevent rebound hyperkalaemia, particularly since the hypokalaemia is due to transcellular shift rather than potassium depletion.

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