ORIGINAL ARTICLE

Thyrotoxic Periodic Paralysis in Azari Iranians

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Thyrotoxic periodic paralysis (TPP) is a fairly common accompaniment of thyrotoxicosis in Orientals. The disorder is a rare complication of thyrotoxicosis in the United States and Europe. There is no published study on the prevalence of hypokalemic periodic paralysis in thyrotoxic Iranian patients. In order to obtain a fairly good estimate, the prevalence of TPP among thyrotoxic patients from the northwestern part of Iran (east Azerbaijan province) was investigated.

Materials and Methods: All new cases of thyrotoxicosis attending the endocrine clinics of Tabriz University of medical sciences were questioned specifically on the occurrence of periodic paralytic attacks. Only patients who had experienced one or more attacks of flaccid paralysis of extremities lasting from a few hours to few days and followed by complete spontaneous or in-hospital recovery were included. Thirty-nine patients were evaluated during paralytic episodes. In 14 cases, diagnosis was based on typical and compatible history given by thyrotoxic patients.

Results: During a 10-year period between 1989 and 1999 a total of 5463 patients were seen with thyrotoxicosis of various etiologies. Of these patients, 4451 (81.5%) were female and 1012 (18.5%) were males. Among this thyrotoxic population, there were 53 proved cases of TPP (4 females and 49 males). All patients were Iranian from the northwestern part of the country; the prevalence of TPP among male patients was 4.8% and among thyrotoxic females 0.08%, with an overall prevalence of 0.97%.

Conclusion: This prevalence rate is one half the rates reported from Japan and China and approximately 10 times the rate reported from the United States. It is concluded that TPP is a relatively common complication of thyrotoxicosis in Azari Iranians. Physicians should be cognizant of this condition to ensure early diagnosis and treatment of a potentially life-threatening but remediable disorder.

Key Words: Thyrotoxicosis, Hypokalemia, Thyrotoxic periodic paralysis

Introduction

Periodic paralysis as a complication of hyperthyroidism is characterized by simultaneous thyrotoxicosis, hypokalemia and paralytic attacks.[1] The trait seems to have a genetic component and it occurs primarily in males of Oriental descent.[1-9] The ethnic predilection of thyrotoxic periodic paralysis (TPP) for Orientals implies a genetic basis for this condition, and the HLA association in TPP is also in support of the hypothesis.[10-12] In Japan, this complication has been reported to occur in some 2% of all thyrotoxic patients.[2] Ninety percent of case reports in literature have come from Japan.[6,7] It occurs in 1.9% of hyperthyroid Chinese population.[4] The disorder has also been described in other Asian populations including patients of Ko-

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rean, Filipino, Vietnamese, Singaporean, Cambodian and Malay ancestry.[5-9,13] The exact prevalence in non-Orientals is not known.[5] It is a rare accompaniment of thyrotoxicosis in the United States and Europe.[5-7] Even in reports from Western nations, the patients afflicted are frequently of Asian origin.[14-20] Although the association of thyrotoxicosis and hypokalermic periodic paralysis has been well known since 1931,[21-22] its diagnosis can be readily overlooked because of a lack of familiarity with the disorder.

There is no published data on the prevalence of thyrotoxic periodic paralysis (TPP) in thyrotoxic Iranian patients. Before this investigation was made, it was apparent to us from our outpatient practice that periodic paralysis commonly complicated thyrotoxicosis in Iranians, but, strangely, this had not been reported in the literature. The aim of this study was to determine the prevalence of TPP in Iranian hyperthyroid patients.

Materials and Methods

During a ten-year period between 1989 and 1999, all new cases of thyrotoxicosis attending the endocrine clinics of Tabriz University of Medical Sciences were questioned specifically about the occurrence of periodic paralytic attacks. Only patients who had experienced one or more attacks of flaccid paralysis of extremities, each lasting from a few hours to few a days and followed by complete spontaneous or in-hospital recovery were included. Thirty-nine patients were evaluated during paralytic episodes. In 14 cases, diagnosis was based on typical and compatible history given by thyrotoxic patients. Serum K^+ was measured during paralytic attacks in 39 patients who were admitted to hospital or seen at emergency departments. The hormonal measurements included serum concentrations of total T_4, total T_3, T_3 resin uptake and TSH. These parameters were measured by radioimmunoassay techniques. Radioiodine uptake was determined at 4 and 24 hours in 31 patients. The diagnosis of thyrotoxicosis was based upon clinical features and compatible thyroid function tests.

Results

During the study period, a total of 5463 patients were seen with thyrotoxicosis of various etiologies in our clinics. Of these patients 4451 (81.5%) were females and 1012 (18.5%) were males. Among this thyrotoxic population there were 53 proved cases with TPP, the prevalence of TPP among male thyrotoxic patients being 4.8% and among thyrotoxic females 0.08%, with an overall prevalence of 0.97% (Table 1). All 53 patients were Azari Iranians from the northwestern part of Iran. There were 49 males and 4 females among patients with TPP (male to female ratio of 12 to 1), who were aged 18 to 55 years with a mean age of 32. Age distribution showed a shift to younger ages compared to that of uncomplicated thyrotoxic patients (mean age of 39.6 years). In 45 patients (85%) the attacks began between the ages of twenty and thirty-nine (Table 2). A positive family history of TPP was recorded in only one case. All patients had clear-cut laboratory evidence of thyrotoxicosis. Graves' disease, diagnosed by clinical finding of diffuse goiter and laboratory data, was the cause of hyperthyroidism in the majority of patients (51 cases). Two patients had nonimmunologic thyroid disease (one had a toxic adenoma and the other had toxic multinodular goiter). All patients had one or more acute episodes of symmetrical flaccid paralysis of the muscles of the extremities and limb girdles. The presenting manifestation was quadriplegia in 42 patients and paraplegia in 11 cases. Onset of paralytic attacks in about 74% of patients was during the night or in the early hours of the morning. Precipitating factors were a heavy carbohydrate meal in 18 patients, strenuous physical activity followed by rest or sleep in 13 cases, and intramuscular injection of a long-acting corticosteroid preparation in 6 patients. The first attack of TPP occurred either with, or a few weeks after, the onset of

Table 1. Prevalence of TPP by sex in Azari Iranians

Sex	No. of cases of thyrotoxico-	No. of cases with TPP	preva-lence of TPP(%)
Male	1012	49	4.8%
Female	4451	4	0.08%
Total	5463	53	0.97%

Table 2. Age of patients at the time of diagnosis of periodic paralysis

	Age groups (years)				
Sex	<20	20-29	30-39	40-49	≥50
Male	1	22	19	6	1
Female	0	3	1	0	0
Total	1	25	20	6	1

thyrotoxic symptoms in 62% of this series. About 30% of our patients had only a few clinical manifestations of thyrotoxicosis. In other words they had mild clinical features of hyperthyroidism. Hypokalemia was the most consistent biochemical abnormality during paralytic attacks. Serum potassium levels ranged from 1.2 to 2.8 mmol/L. More than 50% of the patients were admitted to hospital with initial diagnoses of familial periodic paralysis, hysterical paralysis, Guillain-Barre syndrome, multiple sclerosis, myasthenia gravis and other demyelinating disorders. Paralytic attacks were ultimately resolved by treating the underlying hyperthyroid disease. Following a course of antithyroid treatment for at least 18 months, 42 of 53 patients had a relapse of hyperthyroidism. The attacks of paralysis recurred in 31 of 42 patients who had a thyrotoxic relapse.

Discussion

The first report of periodic paralysis appeared in 1882; a 44-year old man had classical attacks of periodic paralysis for 25 years, and his father had died of a similar attack of paralysis at the age of 54.[23-24] There are many causes of hypokalemic periodic paralysis (HPP). The majority of cases of HPP in the western countries are familial in origin.[25-27] Some sporadic cases of HPP occur in situations associated with loss of body potassium stores as a consequence of diuretic therapy, mineralocorticoid excess, potassium-losing nephropathy, or renal tubular acidosis. In the majority of Asian patients suffering from sporadic form of HPP there is associated thyrotoxicosis, defining the syndrome of thyrotoxic periodic paralysis.[2-4,13,28] A report from Germany in 1902 was the first to describe an association between thyrotoxicosis and HPP.[29] The first association with hyperthyroidism in the United States was reported by Dunlap and Kepler in 1931.[21] It is well known that HPP is associated with some cases of thyrotoxicosis.[1-5] This complication is reported to have a distinct racial distribution. It occurs predominantly in patients of Mongoloid stock.[1-9] In a series of 6333 Japanese thyrotoxic patients, 1.9% had episodes of periodic paralysis, with 8.2% of males and 0.4% of females being afflicted.[2] A similar observation in a large Chinese hyperthyroid population found the prevalence of TPP to be 13% in men and 0.2% in women.[4] More than 90% of cases of TPP reported in world literature have occurred in Orientals.[3-5] The disorder has also been described in other Asian populations including Korean, Filipino, Cambodian, Malay, Thai, Laotian, and Vietnamese.[5-9] TPP is considered to be very uncommon in Caucasians and Blacks.[5-7] Even in reports from western nations, the patients afflicted are frequently of Asian origin.[14-19] The prevalence of TPP in non-Orientals has not been determined.[5] The experience reported from Mayo Clinic for the years 1966 to 1986 suggests a prevalence of 0.1 to 0.2% or about one-tenth that seen in Asian populations.[5,20]

Before this investigation was made it was apparent to us, from our out-patient practice that periodic paralysis commonly complicated thyrotoxicosis in Iranians. In the present study 53, (0.97%) of 5463 thyrotoxic Forty-nine (4.8%) males and 4 (0.08%)

Table 3. TPP in Azari Iranians compared to the international experience with the disorder

Country	Study period	No. of patients with thyrotoxicosis	Patients with TPP (%)	Male (%) TPP	Female (%) TPP
Japan	1937-1956	6333	1.9%	8.2%	0.4%
China	1960-1967	1366	1.8%	13%	0.17%
Iran	1989-1999	5463	0.97%	4.8%	0.08%
USA	1966-1986	8972	0.1%	Not reported	0%

females gave a history of one or more attacks of hypokalemic paralysis. This prevalence rate is one-half the rate reported from Japan[2] and China[4] and approximately 5-10 times the rate reported from United States[5,20] (Table 3).

The other epidemiologic characteristic of TPP is the striking male preponderance ranging from approximately 12:1 to 20:1. TPP occurs 6 to 20 times more commonly in the male than in the female sex.[1-7] Thus, although hyperthyroidism is much more common in women, TPP has a strong predilection for men. As is also the case among the Japanese and Chinese, the disorder was more common in our thyrotoxic males with a male to female ratio of 12 to 1.

Approximately 80% of patients who manifest TPP are aged 20 to 39 years.[2-6] In our series, the majority of patients (85%) were aged between 20 and 39 years (Table 2). This is definitely different from the age distribution of uncomplicated HPP which usually develops in the first two decades of life.

Among patients with TPP, a positive family history of a similar attack was an exception rather than the rule. In his review of the literature, Engel noted a positive family history in only 2% of reported patients with TPP.[3] McFadzean and Yeung, and Yeo et al were not able to obtain a positive family history in their series of 76 patients with TPP.[7,28,30] A similar result was obtained in the present study; a family history of the disorder was recorded only in one of our 53 patients with TPP. Some specific stimuli appear to provoke attacks of hypokalemic periodic paralysis. These precipitating factors are trauma, menses, infection, emotion, physical exertion, heavy carbohydrate load, cold exposure, and administration of epinephrine, thyroid hormones, or corticosteroids.[5-6] The most common scenario is onset of paralysis following a heavy carbohydrate meal or strenuous physical activity followed by rest or sleep.[2-7] In our patients precipitating factors were excessive carbohydrate ingestion in 18 patients, strenuous physical exertion followed by rest in 13 cases, and intramuscular injection of a long-acting corticosteroid preparation preceding paralytic attacks in 6 patients. Corticosteroids were prescribed by general physicians to relieve prodromal symptoms of muscle pains, cramps or stiffness in the affected muscles preceding paralytic attacks by a few hours or days. In approximately 75% of reported cases, the initial attack of paralysis occurred after, or at the time of appearance of symptoms of thyrotoxicosis.[5-7] The first episode of paralysis occurred either with or shortly after the onset of thyrotoxic symptoms in 62% of the present series.

Although it has been suggested that TPP is seen only with Graves' disease, it appears that the specific cause of hyperthyroidism is not a necessary factor for disease expression.[5-7] The disorder has been reported in association with non-Graves' thyrotoxic thyroid diseases.[5] Among our series, 2 patients had toxic nodular goiter.

Results of several studies indicate that the diagnosis of TPP is often delayed and confused with other common causes of flaccid paralysis of extremities because of lack of

familiarity with the disorder.[1,5-7] More than 50% of patients in the present series were admitted to hospital with initial diagnosis of familial hypokalemic periodic paralysis, hysterical paralysis, Guillain-Barre syndrome, multiple sclerosis, myasthenia gravis, and other demyelinating disorders.

In summary, we described here our experience with TPP in an Iranian thyrotoxic population. TPP was found in 53 of 5463 patients with thyrotoxicosis. The prevalence of TPP among male patients was 4.8% and among thyrotoxic females was 0.08%, with an overall prevalence of 0.97%. The results of this study indicate that TPP, a relatively common complication of thyrotoxicosis in the northwestern part of our country, affects predominantly males, and is rarely associated with positive family history, the peak prevalence being in the age groups of 20-29 and 30-39 years. Graves' disease is the most common cause of hyperthyroidism in affected patients. Thyrotoxicosis may be clinically silent. The diagnosis of TPP is often delayed and confused with other causes of muscular paralysis of extremities. Paralytic attacks return with thyrotoxic relapse.

Physicians should be cognizant of TPP to ensure early diagnosis and treatment. A high index of suspicion in the appropriate clinical setting is the cornerstone to early diagnosis. When a young male is initially seen with severe lower extremity muscle weakness or paralysis, TPP should be considered as the most likely diagnosis until proven otherwise. Thyroid function tests should be routinely performed in all patients with hypokalemic paralysis and patients with TPP should receive a definitive treatment for thyrotoxic state.

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