

Thyrotoxic periodic paralysis: an overview

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SUMMARY: Thyrotoxic periodic paralysis (TPP) is a fairly common manifestation of hyperthyroidism in Asian populations, with an incidence of about 1.9% in thyrotoxic patients, but it is rarely diagnosed among Caucasians and blacks in the Western world. The diagnosis often can be made on the basis of the clinical manifestations alone. Sometimes, periodic paralysis precedes hyperthyroidism or occurs in silent hyperthyroidism. As a result, physicians may easily overlook it even when life-threatening hypokalemia is present. The pathophysiology of this disorder is still not well understood. Correction of the thyrotoxic state is the definitive treatment. Potassium supplementation, propranolol, and spironolactone may be helpful both in the acute state and in preventing attacks.

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Thyrotoxic periodic paralysis (TPP) is a fairly common manifestation of hyperthyroidism in Asian populations,¹⁻³ being seen in about 1.9% of patients with hyperthyroidism,⁴ but is rare in Caucasians and blacks in the Western world.⁵ It may precede hyperthyroidism or accompany silent disease, in which case, it may be misdiagnosed even in the presence of life-threatening hypokalemia.⁶ This article reviews the features of this potentially fatal condition.

Clinical Manifestations

The clinical manifestations and biochemical features of TPP are similar to those of familial periodic paralysis (FPP) except for the symptoms related to hyperthyroidism. Patients often suffer recurrent attacks of muscle weakness, predominantly in the lower legs, with the proximal muscles being affected more severely than the distal muscles. Sensory function and mental status are not altered. Paralysis usually is limited to strenuously exercised muscles. Bulbar, ocular, and respiratory muscles are rarely involved, although impairment of respiratory function has been observed.⁷ Deep tendon reflexes are markedly diminished or absent in most patients. Recovery of muscle function is usually in reverse order of the appearance of the paralysis and occurs within 24 hours, although residual weakness and soreness may persist for several days. Neurologic examinations are normal between attacks. The fleeting paralysis is often misdiagnosed as being psychogenic or malingering.

The major biochemical abnormality during an acute attack is hypokalemia, but total potassium stores of serum are not depleted.⁸ Instead, the abnormality is secondary to an intracellular shift of potassium.⁹ The severity of the hypokalemia usually parallels the extent of muscle weakness,^{1,10} although this correlation is not absolute,¹¹ and TPP may occur when the serum potassium concentration is within normal limits.^{1,5,12-15} Under these conditions, paralysis may result directly from abnormal thyroid hormone levels.^{12,14} In addition to hypokalemia, hypophosphatemia and hypomagnesemia are common features of TPP.¹⁶

Some factors may provoke attacks of hypokalemic paralysis, such as ingestion of carbohydrate and strenuous physical activity followed by a period of rest.^{5,17-20} Other triggers include trauma, cold exposure, infection, menses, and emotional stress.²¹ In one patient, TPP followed ingestion of prostaglandin prescribed to induce abortion.²² Paralysis tends to appear on weekends, which maybe attributable to unusual physical activity and diet and to alcohol ingestion. However, most patients suffer periodic paralysis without an obvious triggering stimulus.

The frequency of paralytic attacks is variable. The attacks are common in the summer and rare in the winter,^{1,2,23} a pattern that may be related to increasing consumption of cold, sweet drinks; strenuous exercise; and potassium loss in sweat during warmer weather. In addition, there is a diurnal pattern, with attacks being more frequent at night or in the early morning and rare in the daytime.^{1,2,17,20}

Cardiac problems, such as rhythm disturbances, are common in TPP.^{24,26} Typical changes of hypokalemia are observed on electrocardiography (ECG) during attacks. Hypokalemic electrocardiographic changes appear to predominate in TPP, which included a prominent U-wave, ST depression, and QTc prolongation.²⁴ However, the different ECG findings of TPP may present in other reports.^{25,26} Overall, many abnormal ECG findings have been noted in TPP, such as atrial flutter or fibrillation,^{24,25} sinus tachycardia,^{24,26} atrial and ventricular extrasystole,^{1,25,27} paroxysmal supraventricular tachycardia,¹ ventricular fibrillation⁶ and conduction defect.^{1,24,26,28} have all been reported. In Hsu et al study,²⁶ a new finding of increased QRS voltage is seen in TPP which provided a simple test to use in combination with other ECG parameters, such as sinus tachycardia and AV block in guiding management decisions in cases of clinical suspicion of TPP.

Relation to Thyroid Status

Patients with TPP usually have attacks only when they are in the hyperthyroid state, although rarely, TPP develops when the patient becomes euthyroid.²⁹ The first attack usually occurs with or shortly after the onset of hyperthyroidism symptoms.^{1,3,5,18} Paralytic attacks can be induced by insulin or carbohydrate injection only when patients are hyperthyroid.¹ Paralytic attacks may recur if patients relapse into a thyrotoxic state from euthyroidism. In Orientals, most TPP patients have clinical manifestations of hyperthyroidism preceding or concurrently with periodic paralysis.¹ However, hyperthyroidism has not been obvious in TPP patients in Western series.^{17,18} Several reports describe patients who have had recurrent episodes of periodic paralysis for months or years before the hyperthyroidism was recognized.^{11,20,30,31} A series reported from the Mayo Clinic observed that nearly half of the affected patients had only subtle signs and symptoms of hyperthyroidism in spite of clear-cut biochemical evidence.¹⁸

The severity of paralysis may not correlate with the degree of hyperthyroidism.^{2,11} Some reports suggest that the level of zinc in red blood cells reflects the integrated functional state of the thyroid over the preceding 2 to 3 months, which signifies recent onset of thyrotoxicosis.^{32,33} Therefore, it may be a useful indicator in patients presented with periodic paralysis without clinical symptoms of thyrotoxicosis. To measure the level of zinc in the red blood cells may provide early recognition of patients whose periodic paralysis preceded to hyperthyroidism.

The specific cause of the hyperthyroid state is not a critical factor in the expression of TPP. Although it has been suggested that TPP is seen only with Graves' disease, TPP has been described in patients with a single toxic thyroid adenoma,¹⁸ toxic nodular goiter,³⁴ iodine-induced thyrotoxicosis (Jod Basedow phenomenon),³⁵ silent thyroiditis,³⁶ and thyrotropin-secreting pituitary adenoma.³⁷

Epidemiology

As noted above, TPP occurs predominantly in Asian populations,¹⁻³ the overall incidence being reported to be 1.8% to 8.8%.^{1,4,38} In the Western world, on the other hand, the incidence is as low as to 0.1% to 0.2%.¹⁸ Unlike Graves' disease without TPP, which has a definite female preponderance, TPP is predominantly a disease of males, with the male-to-female ratio ranging from 17:1 to 76:1 in different ethnic groups.^{1,2,4,35,38,39} The male predominance may reflect the action of androgens on Na⁺-K⁺-ATPase activity. The age of onset of TPP is most commonly between 20 and 40 years,^{1,3,5} which is similar to that of thyrotoxicosis.

Genetics

In view of the increased susceptibility of some ethnic populations and the autoimmune basis of Graves' disease, an immunogenetic marker might be available that would identify the population at risk. Indeed, several reports suggest that there is a genetic basis for TPP.^{1,40-43} For example, in a study of a Chinese population, HLA antigens Bw46 and Bw46/B40 occurred frequently in patients with Graves' disease, regardless of whether they had TPP.⁴² On the other hand, HLA A2, Bw22, and Aw19, B17 were seen in some patients with TPP.⁴² However, although another study confirmed the association of HLA Bw46 with Graves' disease in general, it did not demonstrate an excess of A2 or Bw22 in patients with TPP.⁴³ Another Chinese study showed a significant association of haplotypes HLA-B46 and B9 and the allele DQB1*303 with Graves' disease, but the association became weaker in those people who had TPP.⁴⁴ In a Japanese population, HLA DRw8 was found more frequently in patients with TPP than in people without TPP.⁴⁵ However, associations with HLA-B46/B40 or HLA-DRw8 were not seen in another study of Mexican patients.¹¹ In this study, patients with Graves' disease without TPP had a higher frequency of HLA-DR3 than those having TPP,¹¹ although the association between Graves' disease and HLA-DR3 was relatively strong in Caucasians.⁴⁶ Thus, available data cannot establish a definite causal relation between the lack of HLA-DR3 and the development of TPP in patients with Graves' disease.

In the meanwhile, no identified genetic mutation has been identified in patients with TPP in the past. Until recently, Dias da Silva and co-workers reported the identification of a mutation in the potassium channel subunit gene (R83H-KCNE3), which codes for a potassium skeletal muscle channel, in one sporadic patient of TPP.⁴⁷ This genetic mutation is also one of the most common genetic defects seen in patients with FPP. Aside from displaying similar phenotype, there is also similar molecular defect between these two diseases. It is reasonable to classify this two diseases as channelopathies, which is characterized by

mutations in voltage-gated ion channel gene,⁴⁸ although whether TPP is a channelopathy or not remained a controversy.⁴⁹

Pathophysiology

The mechanism responsible for TPP is still unknown, although the association between hypokalemia and the paralysis may provide a clue. Thyroid hormone alters plasma membrane permeability to sodium and potassium, a function that is linked to Na⁺-K⁺-ATPase activity.^{50,51} Thyroid hormone per se (T₄) increases the activity of this enzyme in tissue,¹⁰ resulting in greater intracellular transport of potassium in hyperthyroidism.⁵² Other studies likewise suggest that the sodium pump plays a role in the pathogenesis of TPP.^{53,54} Hyperthyroidism increases tissue responsiveness to beta-adrenergic stimulation,⁵⁵ which is likewise linked to enhanced Na⁺-K⁺-ATPase activity.⁵⁶ This response also accounts for the control of TPP and protection from paralytic attacks that are afforded by non-selective beta-adrenergic blockers.^{19,57} More precisely, beta 2 receptors have been found to be specific to this effect.⁵⁶ Insulin also may activate Na⁺-K⁺-ATPase activity, which explains the relation of periodic paralysis to carbohydrate loads.⁵⁶ Patients with TPP usually have hyperinsulinemia,⁵⁸⁻⁶⁰ which is accompanied by higher Na⁺-K⁺-ATPase activity.⁶⁰ However, elevation of the insulin concentration was not seen in another study.¹⁹

Another feature of potassium metabolism is the diurnal variation in its movement, with an influx of potassium into skeletal muscle at night and an exercise-induced daytime efflux from the intracellular compartment to the extracellular fluid.¹⁷ This pattern may explain why paralytic attacks occur at night. However, hypokalemia may not be the sole cause of the neuromuscular manifestations of TPP. It is clearly a component of TPP but may not be the ultimate mediator. Several other factors may also play roles. For example, it has been suggested that hypophosphatemia and abnormal calcium metabolism mediate TPP.⁶¹ This idea is supported by the observation of neuromuscular symptoms in thyrotoxic normokalemic paralysis associated with glucose- or insulin-induced hypophosphatemia.

The defect of TPP lies in the muscles, rather than in the nerve or neuromuscular junction,¹ as shown by the lack of muscular excitability in response to direct electrical stimulation during attacks of TPP.⁶² There is evidence that the primary defect is in the sarcolemmal membrane.^{5,17,53}

Differential Diagnosis

The typical manifestations of TPP are easily differentiated from those of other types of paralysis. Thus, although TPP is identical in clinical presentation and biochemical features to familial periodic paralysis (FPP), hyperthyroidism is evidenced in patients with TPP. An additional clue is that most patients with FPP are Caucasian,⁵ whereas TPP is seen

in Asian populations.³ Moreover, FPP is autosomal dominant in transmission, so the patient usually has a positive family history. Both types of periodic paralysis predominantly affect males,^{1,4,18,23,35-38} but TPP occurs at a later age than FPP. The simultaneous presence of TPP and FPP is extremely rare. To differentiate FPP from TPP patients with clinically silent thyrotoxicosis, intra-arterial infusion of low doses of epinephrine is of diagnostic value. In FPP, electromyographic picture shows a marked decrease in compound muscle action potential amplitude in response to epinephrine infusion, but not in TPP.^{18,63}

Furthermore, periodic paralysis can be classified into three subgroups according to the level of serum potassium: hypokalemic (Hypo-KPP), normokalemic (Normo-KPP) and hyperkalemic (Hyper-KPP).⁴⁸ They are easy to differentiate from TPP if symptoms of thyrotoxicosis is obvious. Besides, Hyper-KPP patients have characteristically a strong family history, younger onset of disease attack, frequent attack of paralysis, and mostly importantly, a specific neurological presentation, paramyotonia congenita.⁶⁴ Normo-KPP is a rare subgroup whose clinical characteristics is similar to Hyper-KPP, and is considered a variant of Hyper-KPP in a recent report.⁶⁵ It is difficult to differentiate Normo-KPP from TPP with normal serum potassium concentration other than previous mentioned characteristics. In Hypo-KPP, they have similar clinical presentations to hypokalemic TPP except for hyperthyroidism. Intra-arterial infusion of low doses of epinephrine is of diagnostic value. Ethnic factor, family history and genetic background may provide another clue to differentiate Hypo-KPP from hypokalemic TPP.

Hypokalemia and paralysis can occur in other metabolic disorders, such as primary aldosteronism, Bartter or Gitelman's syndrome, and renal tubular acidosis (RTA).⁶⁶⁻⁶⁷ There is a report of simultaneous TPP and RTA.⁶⁹ One should be cautious in making the diagnosis of TPP, especially when clinical manifestations of hyperthyroidism are not obvious. In TPP and FPP, hypokalemia and paralysis are secondary to acute intracellular shift of potassium.⁷⁰ On the other hand, in metabolic disorders, the paralysis may be secondary to excessive renal excretion of potassium.⁷¹

Treatment

Correction of the hyperthyroid state is the definitive treatment for TPP. There is only one report of a patient developing TPP while in the euthyroid state.⁷² During treatment of hyperthyroidism, precipitating factors, such as extreme exertion, alcohol drinking, and carbohydrate overload, should be avoided. Some authors have suggested that large doses of potassium chloride might prevent attacks of paralysis,¹ but recurrent attacks are not consistently prevented by potassium supplementation.^{1,7,35} The value of using supplemental potassium routinely to prevent TPP thus

is questionable. However, it is useful to supply potassium during acute periodic paralysis, especially when complicating hypokalemia is suspected. However, caution is necessary because of the possibility of rebound hyperkalemia.¹⁶

Beta-blockers are used to improve thyrotoxicosis and periodic paralysis, benefits that are related to these drugs' anti-hyperadrenergic effect.³⁰ A large dose of propranolol, either orally or intravenously, may terminate the paralysis and rapidly reverse hypokalemia and hypophosphatemia during an acute attack.^{73,74} In patients with normokalemic TPP, prednisolone is an alternative; this agent may reverse the acute paralytic attack secondary to its inhibitory effect on the release of thyroid hormones.¹²

Several drugs have been tried for prevention of periodic paralysis. Acetazolamide was used for treatment and prophylaxis with good effect in one series,⁷⁵ although variable results were reported by other observers.^{19,30,34,76} It appears that acetazolamide may induct disease onset,¹⁹ worsen the severity of attacks^{30,76} or have no effect.³⁴ Spironolactone may be effective

in preventing acute attacks of paralysis in some patients.¹ On the other hand, propranolol decreases the frequency and attenuates the severity of periodic paralysis in most patients.^{19,29,55} One paper has suggested that beta-blockers be evaluated as first-line therapy if there is no contraindication.⁷³

Summary

TPP is commonly seen in Asian patients with hyperthyroidism but only rare in other populations. The condition should be considered when one is confronted with patients with acute muscle weakness, especially if they are male, young, and Asian. Absence of clinical or previous evidence of thyrotoxicosis does not exclude the diagnosis. Although TPP is usually self-limited, fatal complications can occur during an acute attack. Prompt termination of TPP is therefore advisable. Early recognition and early treatment with K supplementation and beta-blockers are the principles of successful management.

References

1. McFadzean AJ, Yeung R. Periodic paralysis complicating thyrotoxicosis in Chinese. *Br Med J*. 1967;1:451-455.
2. Ko GT, Chow CC, Yeung VT, Chan HH, Li JK, Cockram CS. Thyrotoxic periodic paralysis in a Chinese population. *QJM*. 1996;89:463-468.
3. Engel A. Thyroid function and periodic paralysis. *Am J Med*. 1961;30:327-333.
4. Okinaka S, Shizume K, Iino S, et al. The association of periodic paralysis and hyperthyroidism in Japan. *J Clin Endocrinol Metab*. 1957;17:1454-1459.
5. Yeo PP, O'Neil WC. Thyrotoxicosis and periodic paralysis. *Medical Grand Rounds*. 1984;3:10-25.
6. Fisher J. Thyrotoxic periodic paralysis with ventricular fibrillation. *Arch Intern Med*. 1982;142:1362-1364.
7. Crane MG. Periodic paralysis associated with hyperthyroidism. *Calif Med*. 1960;92:285-288.
8. Shizume K, Shishiba Y, Sakuma M, Yamauchi H, Nakao K, Okinaka S. Studies on electrolyte metabolism in idiopathic and thyrotoxic periodic paralysis. II. Total exchangeable sodium and potassium. *Metabolism*. 1966;15:145-52.
9. Shizume K, Shishiba Y, Sakuma M, Yamauchi H, Nakao K, Okinaka S. Studies on electrolyte metabolism in idiopathic and thyrotoxic periodic paralysis. I. Arteriovenous differences of electrolytes during induced paralysis. *Metabolism*. 1966;15:138-144.
10. Layzer RB. Periodic paralysis and the sodium-potassium pump. *Ann Neurol*. 1982;11:547-552.
11. Nellen H, Mercado M, Mendoza V, Villanueva S, Perez M, Hernandez A, Arellano J. Thyrotoxic periodic paralysis in Mexican mestizo patients: a clinical, biochemical, and HLA-serological study. *Arch Med Res*. 1999;30:74-76.
12. Gonzalez-Trevino O, Rosas-Guzman J. Normokalemic thyrotoxic periodic paralysis: a new therapeutic strategy. *Thyroid*. 1999;9:61-63.
13. Kodali VR, Jeffcote B, Clague RB. Thyrotoxic periodic paralysis: a case report and review of the literature. *J Emerg Med*. 1999;17:43-45.
14. Layzer RB, Goldfield E. Periodic paralysis caused by abuse of thyroid hormone. *Neurology*. 1982;24:949-952.
15. Wu CC, Chau T, Chang CJ, Lin SH. An unrecognized cause of paralysis in ED: thyrotoxic normokalemic periodic paralysis. *Am J Emerg Med*. 2003;21:71-73.
16. Manoukian MA, Foote JA, Crapo LM. Clinical and metabolic features of thyrotoxic periodic paralysis in 24 episodes. *Arch Intern Med*. 1999;159:601-606.
17. Charness ME. Clinical Conferences at the Johns Hopkins Hospital: Hypokalemic periodic paralysis. *Johns Hopkins Med J*. 1978;143:148-153.
18. Kelley DE, Gharib H, Kennedy FP, Duda RJ Jr, McManis PG. Thyrotoxic periodic paralysis: report of 10 cases and review of electromyographic findings. *Arch Intern Med*. 1989;149:2597-2600.
19. Yeung RT, Tse TF. Thyrotoxic periodic paralysis: effect of propranolol. *Am J Med*. 1974;57:584-590.
20. Reisin RC, Martinez O, Moran M, Rovira M, Roccatagliata G, Pardel A, de la Balze AE. Thyrotoxic periodic paralysis in Caucasians: report of 8 cases. *Neurologia*. 2000;15:222-225.
21. Ferreiro JE, Arguelles DJ, Rams H Jr. Thyrotoxic periodic paralysis. *Am J Med*. 1986;80:146-150.
22. Richey SD, Wendel GD Jr. Thyrotoxic hypokalemic periodic paralysis following second-trimester prostaglandin-induced abortion. *Obstet Gynecol*. 1993;82(Suppl 2):696-698.
23. Hamada N, Ito K, Nishikawa Y, et al. Clinical studies on thyrotoxic periodic paralysis. In: Li N, ed. *Current Problems in Thyroid Research from Proceedings of the Second Asia Science Conference*. Science Publishing Co. Inc.; 1983:305.
24. Ee B, Cheah JS. Electrocardiographic changes in thyrotoxic periodic paralysis. *J Electrocardiol*. 1979;12:263-279.
25. Boccalandro C, Lopez L, Boccalandro F, Lavis V. Electrocardiographic changes in thyrotoxic periodic paralysis. *Am J Cardiol*. 2003;91:775-777.
26. Hsu YJ, Lin YF, Chau T, Liou JT, Kuo SW, Lin SH. Electrocardiographic manifestations in patients with thyrotoxic periodic paralysis. *Am J Med Sci*. 2003;326:128-132.
27. Resnick JS, Dorman JD, Engel WK. Thyrotoxic periodic paralysis. *Am J Med*. 1969;47:831-836.
28. Chia BL, Lee KH, Cheah JS. Sino-atrial Wenckebach conduction in thyrotoxic periodic paralysis: a case report. *Int J Cardiol* 1995;47:285-289.
29. Rone JK, Brietzke SA. Euthyroid thyrotoxic periodic paralysis. *Mil Med*. 1991;156:434-436.
30. Conway MJ, Seibel JA, Eaton P. Thyrotoxicosis and periodic paralysis: improvement with beta blockade. *Ann Intern Med*. 1974;81:332-336.
31. Bernard JD, Larson MA, Norris FH Jr. Thyrotoxic periodic paralysis in Californians of Mexican and Filipino ancestry. *Calif Med*. 1972;116:70-74.
32. Yoshida K, Kiso Y, Watanabe T, et al. Erythrocyte zinc concentration in patients with subacute thyroiditis. *J Clin Endocrinol Metab*. 1990;70:788-791.
33. Yoshida K, Kiso Y, Watanabe T, et al. Clinical utility of red blood cell carbonic anhydrase I and zinc concentrations in patients with thyroid diseases. *Metabolism*. (Clin Exp) 1991;40:1048-1051.
34. Norris FH Jr, Clark EC, Biglieri EG. Studies in thyrotoxic periodic paralysis. *J Neurol Sci*. 1972;13:431-442.
35. Ober KP. Thyrotoxic periodic paralysis in the United States: report of 7 cases and review of the literature. *Medicine*. 1992;71:109-120.
36. Tinker TD, Vannatta JB. Thyrotoxic hypokalemic periodic paralysis: report of four cases and review of the literature. *J Okla State Med Assoc*. 1987;80:11-5,76-83.
37. Alings AM, Fliers E, de Herder WW, Hofland LJ, Sluiter HE, Links TP, van der Hoeven JH, Wiersinger WM. A thyrotropin-secreting pituitary adenoma as a cause of thyrotoxic periodic paralysis. *J Endocrinol Invest*. 1998;21:703-706.
38. Satoyoshi E, Murakami K, Kowa H, et al. Periodic paralysis in hyperthyroidism. *Neurology*. 1963;13:746-752.
39. Ghose R, Quail G, King R, Maloney P. Hypokalemic paralysis in remote aboriginal communities. *Aust Fam Physician*. 1996;25:1172-1173.
40. McFadzean AJ, Yeung R. Familial occurrence of thyrotoxic periodic paralysis. *Br J Med*. 1969;1:760.
41. Leung AK. Familial "hashitoxic" periodic paralysis. *J R Soc Med*. 1985;78:638-640.
42. Yeo PP, Chan SH, Lui KF, Wee GB, Lim P, Cheah JS. HLA and thyrotoxic periodic paralysis. *Br Med J*. 1978;2:930.
43. Hawkins BR, Ma JT, Lam KS, Wang CC, Yeung RT. Association of HLA antigens with thyrotoxic Graves' disease and periodic paralysis in Hong Kong Chinese. *Clin Endocrinol (Oxf)*. 1985;23:245-252.

44. Cavan DA, Penny MA, Jacobs KH, Kelly MA, Jenkins D, Mijovic C, Chow C, Cockram CS, Hawkins BR, Barnett AH. The HLA association with Graves' disease is sex-specific in Hong Kong Chinese subjects. *Clin Endocrinol (Oxf)*. 1994;40:63-66.
45. Tamai H, Tanaka K, Komaki G, Matsubayashi S, Hirota Y, Mori K, Kuma K, Kumagai LF, Nagataki S. HLA and thyrotoxic periodic paralysis in Japanese patients. *J Clin Endocrinol Metab*. 1987;64:1075-1078.
46. Allanic H, Fauchet R, Lorey Y, et al. HLA and Graves' disease: an association with HLA-DRw3. *J Endocrinol Metab*. 1980;51:863-867.
47. A mutation in the KCNE3 potassium channel gene is associated with susceptibility to thyrotoxic hypokalemic periodic paralysis. *J Clin Endocrinol Metab*. 2002;87:4881-4884.
48. Ptacek LJ, Bendahhou S. Ion channel disorders of muscle. In: Karpati G, Hilton-Jones D, Griggs RC, eds. *Disorders of voluntary muscle*. 7th ed. Cambridge: Cambridge University Press; 2001:604-635.
49. Gallagher EJ. Is thyrotoxic periodic paralysis a "channelopathy"? *J Emerg Med*. 1999;17:123-127.
50. Rubython EJ, Cumberbatch M, Morgan DB. Changes in the number and activity of sodium pumps in erythrocytes from patients with hyperthyroidism. *Clin Sci (Lond)*. 1983;64:441-447.
51. Haber RS, Loeb JN. Effect of 3,5,3'-triiodothyronine treatment on potassium efflux from isolated rat diaphragm: role of increased permeability in the thermogenic response. *Endocrinology*. 1982;111:1217-1223.
52. Kubota K, Ingbar SH. Influences of thyroid status and sympathoadrenal system on extrarenal potassium disposal. *Am J Physiol*. 1990;258:E428-435.
53. Chan A, Shinde R, Chow CC, Cockram CS, Swaminathan R. In vivo and in vitro sodium pump activity in subjects with thyrotoxic periodic paralysis [erratum at *BMJ* 1992;304:226. *Br Med J*. 1991;303:1096-1099.
54. Hofmann WW, Denys EH. Effects of thyroid hormone at the neuromuscular junction. *Am J Physiol*. 1972;223:283-287.
55. Levey GS, Klein I. Catecholamine-thyroid hormone interactions and the cardiovascular manifestations of hyperthyroidism. *Am J Med*. 1990;88:642-646.
56. Sterns RH, Spital A. Disorders of internal potassium balance. *Semin Nephrol*. 1987;7:399-415.
57. Feely J. Potassium shift in thyrotoxic periodic paralysis. *Postgrad Med J*. 1981;57:238-239.
58. Shishiba Y, Shimizu T, Saito T, Shizume K. Elevated immunoreactive insulin concentration during spontaneous attacks in thyrotoxic periodic paralysis. *Metabolism*. 1972;21:285-290.
59. Lee KO, Taylor EA, Oh VM, Cheah JS, Aw SE. Hyperinsulinaemia in thyrotoxic hypokalemic periodic paralysis. *Lancet*. 1991;337:1063-1064.
60. Chan A, Shinde R, Chow CC, Cockram CS, Swaminathan R. Hyperinsulinaemia and Na⁺-K⁺-ATPase activity in thyrotoxic periodic paralysis. *Clin Endocrinol (Oxf)*. 1994;41:213-216.
61. Au KS, Yeung RT. Thyrotoxic periodic paralysis: periodic variation in the muscle calcium pump activity. *Arch Neurol*. 1972;26:543-546.
62. Puvanendran K, Cheah JS, Wong PK. Electromyographic (EMG) study in thyrotoxic periodic paralysis. *Aust N Z J Med*. 1977;7:507-510.
63. Engel AG, Lambert EH, Rosevear JW, Tauxe WN. Clinical and electromyographic studies in a patient with primary hypokalemic periodic paralysis. *Am J Med*. 1965;38:626-640.
64. Okuda S, Kanda F, Nishimoto K, Sasaki R, Chihara K. Hyperkalemic periodic paralysis and paramyotonia congenita--a novel sodium channel mutation. *J Neurol*. 2001;248:1003-1004.
65. Chinnery PF, Walls TJ, Hanna MG, Bates D, Fawcett PR. Normokalemic periodic paralysis revisited: does it exist? *Ann Neurol*. 2002;52:251-252.
66. Lin SH, Lin YF, Halperin ML. Hypokalemia and paralysis. *QJM*. 2001;94:133-139.
67. Stedwell RE, Allen KM, Binder LS. Hypokalemic paralysis: a review of the etiologies, pathophysiology, presentation, and therapy. *Am J Emerg Med*. 1992;10:143-148.
68. Ahlawat SK, Sachdev A. Hypokalaemic paralysis. *Postgrad Med J* 1999;75:193-197.
69. Szeto CC, Chow CC, Li KY, Ko TC, Yeung VI, Cockram CS. Thyrotoxicosis and renal tubular acidosis presenting as hypokalaemic paralysis. *Br J Rheumatol*. 1996;35:289-291.
70. Sterns RH, Cox M, Feig PU, Singer I. Internal potassium balance and the control of the plasma potassium concentration. *Medicine (Baltimore)*. 1981;60:339-54.
71. Halperin ML, Kamel KS. Potassium. *Lancet*. 1998;352:135-140.
72. Gandara DR, Fariss BL. Persistence of periodic paralysis following treatment of thyrotoxicosis: case report. *Mil Med*. 1979;144:337-338.
73. Lin SH, Lin YF. Propranolol rapidly reverses paralysis, hypokalemia, and hypophosphatemia in thyrotoxic periodic paralysis. *Am J Kidney Dis*. 2001;37:620-623.
74. Birkhahn RH, Gaeta TJ, Melniker L. Thyrotoxic periodic paralysis and intravenous propranolol in the emergency setting. *J Emerg Med*. 2000;18:199-202.
75. Norris FH Jr. Use of acetazolamide in thyrotoxic periodic paralysis. *N Engl J Med*. 1972;286:893.
- Shulkin D, Olson BR, Levey GS. Thyrotoxic periodic paralysis in a Latin-American taking acetazolamide. *Am J Med Sci*. 1989;297:337-338.