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CASE

Thyrotoxic Hypokalemic Periodic Paralysis in a Turkish Male with Graves' Disease

A Rare Case Report and Review of the Literature

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Thyrotoxic hypokalemic periodic paralysis (THPP) is a very rare complication of thyrotoxicosis in whites, but is more frequently reported in individuals of Asian descent. Hypokalemia, with associated flaccid paralysis, and signs of hyperthyroidism, are the hallmark. We have reported a case of a 28-yr-old white man with Graves' disease presenting with a 2-wk history of episodic flaccid quadriplegia. Physical examination disclosed a resting tachycardia and symmetrical, proximal weakness involving both arms and legs. Electrocardiogram and electrolyte analysis showed a severe hypokalemia, and thyroid function tests revealed hyperthyroidism. The patient was diagnosed as having Graves' hyperthyroidism and THPP. Paralysis resolved with potassium supplements. He was treated with propranolol and, subsequently, methimazole. He had no further episodes of hypokalemic paralysis. To the best of the author's knowledge, and after a Medline search, THPP has not been described previously in a Turkish man.

Key Words: Hyperthyroidism; hypokalemia; periodic paralysis; Turkish man.

Introduction

Thyrotoxic hypokalemic periodic paralysis (THPP) is a rare endocrine disorder resulting from the excessive release of thyroid hormones *(1,2)*. The prevalence as determined in a study of hyperthyroid patients in North America was 0.1–0.2% *(3)*. THPP is a common cause of sudden onset weakness in young people of Asian ethnic origin, and rarely occurs in Caucasians *(4)*.

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Hypokalemia is a common condition occurring in approx 5% of all hospitalized patients; however, severe hypokalemia, defined as <2.5 mmol/L (3.5–5.0 mmol/L), is an uncommon but acutely disabling and potentially life-threatening disorder *(5)*.

THPP is an uncommon cause of paralysis in the general population. It occurs in 13–24% of Orientals with thyrotoxicosis *(6)*. In this race it occurs 70 times more frequently in males than females *(6)* and usually occurs between the ages of 20 and 40 yr reflecting the age of onset of thyrotoxic Graves' disease *(7)*. To our knowledge, and after a Medline search using the key words hypokalemia, thyrotoxicosis, thyrotoxic periodic paralysis, and Turkish male, this is the first described case of THPP in a white Turkish man.

Case Report

A 28-yr-old man was admitted to the emergency department of our hospital with a chief complaint of extreme weakness in his arms and legs. The patient awoke in the morning unable to move his lower extremites (flaccid paralysis), with extreme weakness of his upper extremities after a carbohydrate-rich meal the previous evening, and had been brought to the hospital with difficulty. He described 2 wk of progressive weakness with episodic exacerbations (two times in last 2 wk) that interfered with his ability to ambulate, rise from a sitting position, and climb stairs. He also had hyperthyroid symptoms (heat intolerance, nervousness, sweating, palpitation, and weight loss). He also had severe hyperthyroidism for 2 mo, and had been receiving propylthiouracil therapy (300 mg/d). He had no significant familial medical history.

On admission, the patient was tachycardic to 110 beats/min, with a blood pressure of 160/60 mmHg. His temperature was 36.8°C. On eye examination, lid retraction was present, but exophthalmos and lid lag were absent. Examination of the neck revealed a diffusely enlarged thyroid gland without palpable nodules or bruit. The patient's skin was warm, moist, and well perfused. He had a fine tremor. On neurological examination, cranial nerves II–XII were intact.

Tendon stretch reflexes were absent at the knee bilaterally and diminished at the biceps. Hip and arm flexors exhibited 1/5 strength bilaterally. Quadriceps strength was 1/5 bilaterally. Distal strength was subjectively reduced, but 5/5 bilaterally on examination. The patient was unable to sit from a supine position. The rest of the examination was normal. An electrocardiogram (ECG) showed a regular sinus tachycardia and ST segment depression with prominent U waves typical of hypokalemia.

Laboratory investigation revealed a serum potassium level of 1.5 mmol/L, a sodium of 142 mmol/L, chloride of 107 mmol/L, glucose 143 mg/dL, blood urea nitrogen 20 mg/dL, creatinine 0.7 mg/dL, calcium 10 mg/dL, and phosphate 3.2 mg/dL. Thyroid function testing revealed an elevated total T_3 (9.0 ng/mL; normal 0.6–1.81), total thyroxine (T_4) (25.4 μg/dL; normal 4.5–10.9), free T_3 (20 pg/mL; normal 2.3–4.2), and free T_4 (10.2 ng/dL; normal 0.89–1.76). Thyroid stimulating hormone was suppressed (0.01 mIU/L). Thyroid autoantibodies showed an prominent elevated TSH receptor antibody (45.5 IU/L; normal 0–10), thyroglobulin antibody (373 IU/mL; normal 0–40), and thyroid peroxidase antibody (72.7 IU/mL; normal 0–40).

Treatment was started with intravenous administration of potassium chloride at 10 mmol/h and oral potassium chloride at 40 mmol every 8 h. Muscle weakness and hypokalemia resolved within 20 h after the patient received a total of 340 mmol of potassium. Minimal rebound hyperkalemia occurred by potassium therapy. Potassium level rose to 5.6 mmol/L, then returned to normal level (4.2 mmol/L).

The patient was started on methimazole 45 mg/d and propranolol 80 mg/d, and was advised to avoid strenuous exercise and carbohydrate-rich meals. He was discharged 3 d later without recurrence of weakness. He was clinically and biochemically euthyroid at the second month after initiation of methimazole treatment, and has remained so thereafter.

Discussion

The first reported case of THPP appeared in the German literature in 1902 by Rosenfield *(8)*. The first case reported in English was in 1931 from the Mayo Clinic *(9)*. Ober *(10)* reported seven cases and provided an excellent review of the literature in 1992. THPP predominantly affects young East Asian and Japanase men with a prevalence of 2–10% *(10,11)*. It was also been described in (i) Asian women *(12)*, (ii) Hispanics *(13)*, (iii) American Indians *(14)*, Mediterranean *(15)*, and Caucasians *(4,16)*. THPP predominantly affects men, with a 20 to 1 ratio, despite the higher incidence of thyrotoxicosis in females *(16)*. It usually presents in the second to fourth decades, consistent with the age distribution of thyrotoxicosis *(11)*. Usually, there is no familial history of periodic paralysis.

THPP is also a rare cause of hypokalemia. It is characterized by recurrent attacks of hypokalemia and bilateral lower limb paralysis associated with thyrotoxicosis. Attacks most commonly occur at night while the patient is in bed, following exertion or ingestion of a large carbohydrate load. Other precipitant factors reported include (i) ingestion of exogenous thyroxine, (ii) stress, and (iii) extremes of temperature *(17)*. Alcohol, trauma, cold exposure, infection, menses are frequently described as other triggers *(18)*. The paralysis can vary from mild to severe, and the lower extremites are usually the most severely affected by pain and cramps in muscles are reported *(17)*. Deep tendon reflexes are depressed in most patients *(19)*.

Although the condition is rarely life threatening and infrequently involves the cranial nerves, deaths from respiratory paralysis and cardiac failure have been reported *(5)*. The paralysis resolves over a period of 3–36 h, usually in the reverse order of its appearance. Serious morbidity is rare, but includes dysrhythmias, ventilatory failure, and death *(20,21)*.

The principal biochemical abnormality is hypokalemia *(17)*. However, both normokalemic (4.0 mmol/L) and hypokalemic cases have been reported *(22,23)*. The lowest reported serum potassium level was 1.3 mmol/L *(11,24)*. The Asian experience suggests that the hyperthyroidism is usually obvious, but this is not so in many reports in the western literature *(1,10,25,26)*. In our case, characteristically, thyroid function studies are consistent with hyperthyroidism; TSH is low, often undetectable, and T_3 and T_4 levels are markedly elevated.

Patients presenting with THPP commonly have Graves' disease; however, thyrotoxicosis of any etiology can trigger an acute attack *(23)*. The most common cardiovascular finding is sinus tachycardia; however, atrial fibrillation with variable atrioventricular nodal blockage and ventricular arrhythmias are rarely associated *(5)*.

The pathophysiolgy of TPP is not well understood. Sodium, chloride, calcium, and potassium channels on cell membranes form the basis for membrane excitability and muscle contraction. Disruption of any of these cellular transport mechanisms—particularly involving the potassium ion channel—may cause abnormalities in muscle contractibility, and paralysis. The principal defect in THPP is an accentuated rise in intracellular potassium. This is due in most cases to genetically based defects in the Na+/K+ ATPase pump *(5)*. Thyroid hormone increases activity of the cell membrane Na+/K+ ATP pump. Excess circulating thyroid hormone causes hyperstimulation of the Na+/K+ pump *(6)*. Furthermore, patients with THPP have an 80% greater pump activity than their counterparts with hyperthyroidism alone *(24)*. A hyperactive Na+/K+ ATP pump that exchanges Na+ (pumped out of the cell) for K+ (pumped into the cell) may account for the hypokalemia seen in THPP. Hypokalemia in THPP results from a potassium shift into cells and not total-body depletion of potassium. In all patients with hyperthyroidism, with or without periodic paralysis, sodium–potassium ATPase activity returns to normal with establishment of the euthyroid state *(6,7)*.

Thyroid hormone sensitizes the cell to beta-adrenergic stimulation of the Na+/K+ ATPase *(27)*. This hypersensitivity is potentiated by epinephrine, which exacerbates the attacks, and attenuated by propranolol *(1)*. Beta-2 blockers are also known to blunt epinephrine-induced intracellular shifts of potassium *(24)*. Similar to epinephrine, insulin stimulates the Na+/K+ ATP, which may explain why the attacks are often preceded by a large carbohydrate load or a period of rest after exercise *(28)*. For this reason, glucose infusions should be avoided in TTP as glucose increases endogenous insulin secretion and can exarbate the intracellular shift, further reducing serum potassium levels *(29)*.

Although it is known that treatment of hyperthyroidism prevents periodic paralysis, there have been no controlled trials regarding the optimum management of acute muscle weakness associated with THPP *(1)*. THPP is a self-limiting disorder that will spontaneously resolve in 3–36 h. Treatment with intravenous or oral potassium will shorten attacks of paralysis and will prevent cardiopulmonary complications. Griggs and co-workers have shown a paradoxical fall in serum potassium levels after intravenous potassium supplementation when using dextrose or sodium chloride solution. This has been attributed to insulin-mediated distribution of potassium in the former case and renal potassium wasting in the latter *(29)*. Management of the patient during an episode of hypokalemic paralysis requires cardiac and electrolyte monitoring because of the risk of cardiac arrythmia, although cardiac arrest is uncommon *(30)*. Propranolol is an accepted therapy for prophylaxis of accute attacks and recent cases have advocated its use in the treatment of the accute attacks *(31)*. By reversing the adrenergic overstimulation of the Na+/K+ ATPase, propranolol blocks the intracellular sequestration of potassium. The risk of recurrent episodes of hypokalemic paralysis may be reduced by beta-blockade and avoidance of strenuous exercise and carbohydrate-rich meals and treatment with antithyroid drugs. Once patients are euthyroid, they are not at risk of hypokalemic paralysis *(7)*.

In conclusion, thyroid function tests should be undertaken routinely in any patient presenting with unexplained muscle weakness, and THPP should be considered in the differential diagnosis. It has been observed almost only in Asians; however, with this case and others reported, we believe that it should be considered as a cause of muscular paralysis also in Caucasians. Early treatment of the underlying thyrotoxicosis will prevent future attacks of acute hypokalemic paralysis. To the best of our knowledge this is the first reported case of TPP in the Turkey.

References

1. Walters, W. A., Han, S. W., and Schoffstall, J. (1999). *J. Emerg. Med.* **17,** 47–51.
2. Lin, S. H. (2005). *Mayo Clin. Proc.* **80,** 99–1205.
3. Paul, B., Hirudayaraj, P., and Baig, M. W. (2003). *Emerg. Med. J.* **20,** E7.
4. Biering, H., Bauditz, J., Pirlich, M., Lochs, H., and Gerl, H. (2003). *Horm. Res.* **59,** 301–304.
5. Tran, H. A., Kay, S. E., Kende, M., Doery, J. C. G., Colman, P. G., and Read, A. (2003). *Int. Med. J.* **33,** 91–94.
6. Chan, A., Shinde, R., Chow, C. C., Cockram, C. S., and Swaminathan, R. (1991). *BMJ* **303,** 1096–1099.
7. Dixon, A. N. and Jones, R. (2002). *Postgrad. Med.* **78,** 687–688.
8. Rosenfeld, M. (1902). *Berl. Klin. Wochnschr.* **39,** 538.
9. Engel, A. G. (1961). *Am. J. Med.* **30,** 327–333.
10. Ober, P. K. (1992). *Medicine* **71,** 109–120.
11. Stedwell, R. E., Allen, K. M., and Binder, L. S. (1992). *Am. J. Emerg. Med.* **10,** 143–148.
12. Szeto, C. C., Chow, C. C., Li, K. Y., Ko, T. C., Yeung, V. T., and Cockram, C. S. (1996). *Br. J. Rheumatol.* **35,** 289–291.
13. Zumo, L. A., Terziyan, C., and Brannan, T. (2002). *J. Natl. Med. Assoc.* **94,** 383–386.
14. DiBaise, J. (1995). *Iowa Med.* **85,** 291–292.
15. Michail, S., Dagounaki, P., Stamadiadis, D., Vaiopoulos, G., Stathakis, C., and Vosnides, G. (1996). *Neprol. Dial. Transplant.* **11,** 1634–1636.
16. Celani, M. F., Bonati, M. E., and Cavalli, M. (1995). *J. Endocrinol. Invest.* **18,** 228–231.
17. Miller, J. D., Quillian, W., and Cleveland, W. W. (2004). *Pediatrics* **100,** 412–124.
18. Mellgren, G., Bleskestad, I. H., Aanderud, S., and Bindoff, L. (2002). *Thyroid* **12,** 77–80.
19. Norris, F. H. Jr., Clark, E. C., and Biglieri, E. G. (1971). *J. Neurol. Sci.* **13,** 431–432.
20. Fisher, J. (1982). *Arch. Intern. Med.* **142,** 1362–1364.
21. Jackman, R. L. and Jones, R. E. (1964). *Arch. Intern. Med.* **113,** 657–664.
22. Kodali, V. R. R., Jeffcote, B., and Clague, R. B. (1999). *J. Emerg. Med.* **17,** 43–45.
23. Kelley, D. E., Gharib, H., Kennedy, F. P, Duda, R. J. Jr., and McManis, P. G. (1989). *Arch. Intern. Med.* **149,** 2597–2600.
24. Tassone, H., Moulin, A., and Henderson, S.O. (2004). *J. Emerg. Med.* **26,** 157–161.
25. Ober, P. K. and Hennessy, J. F. (1981). *Arch. Intern. Med.* **141,** 1225–1227.
26. Liu, Y.-C., Tsai, W-S., Chau, T., and Lin, S.-H. (2004). *Am. J. Med. Sci.* **327,** 264–267.
27. Marx, A., Ruppersburg, P., Pietrzyk, C., and Rudel, R. (1989). *Muscle Nerve* **12,** 810–815.
28. Chan, A., Shinde, R., and Chow, C. C. (1994). *Clin. Endocrinol.* **41,** 213–216.
29. Griggs, R. C., Resnick, J., and Engle, W. K. (1983). *Arch. Neurol.* **40,** 539–540.
30. Bergeren, L. and Sternbach, G. L. (1988). *Ann. Emerg. Med.* **127,** 843–845.
31. Birkhahn, R. H., Gaeta, T. J., and Melniker, L. (2000). *J. Emerg. Med.* **18,** 199–202.