RESEARCH LETTER

Thyrotoxic Periodic Paralysis

H Singh, Sunil Garg, Ramesh Kumar, K H Virendra, Sushil Jain, Rahul Handa

The spectrum of muscular disorders in hyperthyroidism coalase due to a) directly related to hyperthyroidism which may lead to thyrotoxic myopathies or thyrotoxic periodic paralysis b) Due to associated orbitopathy or myasthenia gravis (1). Of these TPP is reversible rare disorder characterized by progressive symmetrical weakness leading to paralysis of extremeties, hypokalemia (often with potassium levels<3.0 meq/l) and hyperthyroidism.These episodes usually occurs after heavy exertion or a high carbohydrate meal, followed by prolonged rest (1,2). TPP is an endocrine emergency because arrythmias and respiratory failures may occur and high degree of suspicion is essential as overt features of hyperthyroidism are usually lacking (1,2). A case report of TPP along with review of literature is being presented.

A 38 year old man presented to the Emergency department in the early hours of morning complaining of sudden generalized weakness of all the four limbs. He was fully alert and coherent. History data revealed similar attack to have occurred nine years back , which spontaneously regressed with in few hours. The patient had not been hospitalized before.The patients had no history of palpitations, nervousness, and hyperorexia with weight loss. On examination at the Emergency Unit, the patients was immobile due to tetraperesis, concious, afebrile and eupenic with moist skin.The pulse rate was 116/minute, sinus rhythm and blood pressure was 130/80 mm Hg with moist skin. Higher functions were normal and there were no cranial nerve symptoms. The power was grade 2/5 in all four limbs and deep tendon reflexes were depressed.There were no sensory involvement. Respiratory rate was 20 breaths per minute,saturation of 100% on room air and temperature of 99 degree F. The patients had no signs of hyperthyroidism except for the presence of fine tremors and moist skin. Complete blood count,ESR, blood glucose, creatinine, transaminases, bilirubin were normal; potassium was 2.1mEq/l (normal range 3.5-5.0mEq/L). serum calcium 10.1mg/dl (normal range 9-11 mg/dl), serum phosphorus 2.6 mg/dl (normal range 2.5-4.5 mg/dl). Arterial blood gases and acid-base balance were with in the normal range. Urine: pH 6.5; specific gravity 1.015; sediment normal; 24-hour urine protein negative; urinary electrolytes were also in the normal range. Thyroid hormones: T3 3.65 ng/ml (0.60-1.81); T4 11.90ug/dl (4.50-10.90); TSH 0.01uIU/mL (0.35-5.50), indicating hyperthyroidism. Thyroid peroxidase antibodies were positive. Thyroid ultrasonography indicated bilateral enlargement of thyroid glands with altered echotexture and increased blood flow on color Doppler. His ECG showed sinus tacycardia with U waves.Upon admission ,the patients received 40 mmol of intravenous potassium chloride,which resulted in complete regression of tetraperesis.The treatment of hyperthyroidism was started with carbamizole and propranolol and the patient being discharged. After one day of discharge the patient again admitted with the same complaints and managed with the same protocol. The incidence of TPP is highest among Asians, however, with globalisation and immigration, TPP is no longer confined to specific geographic areas and has been reported increasingly in other ethnic groups (2). Approximately 2% of patients with thyrotoxicosis in China and Japan reportedly have TPP when compared to 0.1% to 0.2% in nonasian population (2). Further, despite a higher incidence of thyrotoxicosis in women, TPP occurs predominantly in men; the male : female ratio is approximately 20:1 (2). The racial differences and male predominance in TPP are intriguing. The presence of different HLA antigen subtypes- A, B22, AW19 and DRW8 in Asian population may make such person susceptible to TPP (1,2).

Grave's disease is the most common association with TPP although it has been reported with almost any form of thyrotoxicosis, including nodular goiter, thyroiditis, amiodarone induced hyperthyroidism and thyroxine overdosage (1,2). Hypokalemia, hypophosphotemia and mild hypomagnesemia are characteristic of TPP.The pathogenesis of TPP is related to thyrotoxicosis per se, rather than to the specific disease causing hyperthyroidism. The Na+, K+- ATPase pump activity in platelets and skeletal muscle cells was increased in patients with thyrotoxicosis and periodic paralysis compared with patients with thyrotoxicosis and no paralysis (2). Excess Na+,K+ ATPase activation in hyperthyroidism has been the cornerstone of the pathogenesis, as this pump stimulates the exit of sodium ions out of cell and couples it with entry of K+ ions into the cell (4). Thyrotoxicosis results in a) hyperadrenergic

From the Department of Medicine. Pt. B.D.Sharma , University of Health Sciences, Rohtak (Haryana)-India
Correspondence to : Dr. H Singh Professor, Dept. of Medicine. Pt. B.D.Sharma , University of Health Sciences, Rohtak (Haryana)-India

state (due to catecholamines secretion, increased sensitivity and molecular similarities that exist between thyroid hormone and catecholamines) b)increased number and sensitivity of ß receptors. Both of these lead to increased Na+, K+- ATPase pump activity (4).Thus, primary defect in TPP is an intracellular sequestration of potassium with normal potassium stores in body 1. Another theory, is that TPP is a channelopathy. Kung et al recently reported that 3 novel single nucleotide polymorphism in Ca (V)1.1 (calcium channel gene). These single nucleotide polymorphisms lie at or near the thyroid hormone- responsive element, this may affect the binding affinity of the thyroid hormone- responsive element and modulate the stimulation of thyroid hormone on calcium(V)1.1. Nevertheless, a genetic analysis on skeletal muscle Na+, K+-ATPase has not yet been investigated thoroughly (5).Unike Familial periodic paralysis (FPP) a positive family history is lacking in TPP and TPP develops later in life affecting males (androgen stimulates Na+,K+ATPase activity (1,2,7). Clinical features may begin insidiously with a prodrome of cramps, aches and muscle stiffness. The paralysis is usually symmetrical (like FPP), proximal muscles of the limbs (lower more than upper) and trunk muscles are involved wlth sparing of higher mental functions, cranial nerves and the sensory system. Attacks can be precipitated by a)high carbohydrate intake (postmeal hyperinsulin stimulates potassium movement into the cell (1,2). b) Sleep (due to nocturnal potassium influx into muscle (8), c)Unusual exertion (increased catecholamines and beta adrenergic stimulation (1,2), d) Others like infection, diarrhoea, thyroid hormone or alcohol abuse.

Spontaneous or induced attacks do not occur in person whose hyperthyroidism has been corrected (1,2). Patients can present with respiratory failure, cardiac arrythmias and thyrotoxicosis crisis. Deep tendon reflexes are depressed in most patients. Respiratory muscles are usually, but not always, spared. Recovery can be spontaneous after 3-36 hours, and may be hastened by potassium administration (1,2).Between the attacks the subjects are normal and do not show persistent weakness characteristics of thyrotoxic myopathy (1,2).TPP should be considered in differential diagnosis of any acute episode of motor paralysis in young male patients. The absence of ocular and respiratory involvement differentiates TPP from myasthenia gravis and Gullian Barre Syndrome (9,10). Barium poisoning needs to be ruled out (10). FPP usually presents before 2nd decade, with no male predeliction and has a positive family history .There is an increase in nonaldosterone mineralocorticoids and K+ shift independent of Na+,K+ATPase (10). Other causes of hypokalemia like reduced intake, gastrointestinal losses, intracellular potassium shift (metabolic alkalosis, insulin adrenergic agonists overdosage), renal losses (diuretics, aminoglycosides, penicillin, hyperaldosteronism, renal tubular acidosis) and some familial disorders like familial hypokalemic periodic paralysis, congenital androgenital syndrome, Littles disease should be ruled out (2).Since the potassium stores are normal in patients with TPP, the aim of potassium supplementation is to normalize the plasma potassium concentration instead of repairing a potassium deficit (1,2). Low dose K+ supplementation rather than aggressive high dose infusion could will be preffered treatment in future as reports have suggested that K+ infused at 10meq/hr more than controls are associated with a two fold shorter period of recovery, but with a high incidence of rebound hyperkalemia (1,2). Well designed randomized studies will clarify wheather a combination of low dose K+ supplementation along with a nonselective betablockade (by its heart rate and K+ effect induced by beta receptors) will become therapy of choice in future (1,2).Prophylactic K+ is ineffective as K+ levels are usually normal between the attacks. It must be noted that acetazolamide, a drug used for FPP must not be used for TPP , as it worsens the attacks (2,3). Definitive therapy of TPP is the correction of hyperthyroidism, which can be achieved by antithyroid drugs, surgery or radioiodine therapy depending upon etiology of thyrotoxicosis (1,2). About two weeks of antithyroid drugs might be necessary before the risk of developing TPP has been ameliorated (3).

References

1. Unikrishan AG. Muscular disorders in hyperthyroidism. In. Medicine update 2006 (Edt). B K Sahay published by Association of Physicians of India 2006.pp.215-21.
2. Shih- HL. Conscise review for clinicians- Thyrotoxic Periodic Paralysis. *Mayo clin Proc* 2005;41;99-102.
3. Nilachandra L, Joy Singh AK, Akoijam B, Singh NB. Hypokalemic thyrotoxic periodic paralysis in females- a report of two cases with review. *IJPMR* 2004; 48-51.
4. Chan A, Shinde R, Chow C, Cockram C, Swaminathan R. In vivo and in vitro sodium pump activity in subjects with thyrotoxic paralysis. *BMJ* 1991; 303: 1096-99.
5. Kung AWC, Lau KS, Fong GCY, Chan V. Association of novel single nucleotide polymorphisms in calcium channel a 1 subunit gene (ca (V) 1.1) and thyrotoxic periodic paralysis. *J clin Endocrinol Metab* 2004; 89: 1340-45.
6. Vergles MJ, Ostricki B, Galesie K, Skoro M, Zelenika D. Thyrotoxic periodic paralysis: a case report. *Acta Clin Croat* 2002; 41: 99-102.
7. Charness ME, Johns RJ. Hypokalemic periodic paralysis. *Johns Hopkins Med J* 1978; 143: 148-53 .
8. Dixon AN, Jones R. Thyrotoxic periodic paralysis in a white woman. *Postgrad Med J* 2002; 78: 687-88.
9. Wong P. Hypokalemic thyrotoxic periodic paralysis; a case series. *Can J Emerg Med* 2003; 5(5): 353-55.
10. Paul B, Hirudayaraj P, Baig MW.Thyrotoxic periodic paralysis; an unusual presentation of weakness. *Emerg Med J* 2003; 20: 7