Thyrotoxic periodic paralysis triggered by β_2-adrenergic bronchodilators

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ABSTRACT

Hypokalemic periodic paralysis is the most common form of periodic paralysis and is characterized by attacks of muscle paralysis associated with a low serum potassium (K^+) level due to an acute intracellular shifting. Thyrotoxic periodic paralysis (TPP), characterized by the triad of muscle paralysis, acute hypokalemia, and hyperthyroidism, is one cause of hypokalemic periodic paralysis. The triggering of an attack of undiagnosed TPP by β_2-adrenergic bronchodilators has, to our knowledge, not been reported previously. We describe two young men who presented to the emergency department with the sudden onset of muscle paralysis after administration of inhaled β_2-adrenergic bronchodilators for asthma. In both cases, the physical examination revealed an enlarged thyroid gland and symmetrical flaccid paralysis with areflexia of lower extremities. Hypokalemia with low urine K^+ excretion and normal blood acid-base status was found on laboratory testing, suggestive of an intracellular shift of K^+, and the patients' muscle strength recovered at serum K^+ concentrations of 3.0 and 3.3 mmol/L. One patient developed hyperkalemia after a total potassium chloride supplementation of 110 mmol. Thyroid function testing was diagnostic of primary hyperthyroidism due to Graves disease in both cases. These cases illustrate that β_2-adrenergic bronchodilators should be considered a potential precipitant of TPP.

RÉSUMÉ

La paralysie périodique hypokaliémique est la forme la plus fréquente de paralysie périodique, et elle se caractérise par des accès de paralysie musculaire, associés à de faibles taux sériques de potassium (K^+) et attribuables à un passage soudain des ions dans le compartiment intracellulaire. La paralysie périodique thyrotoxique (PPT), qui se caractérise par la triade de signes suivants, paralysie musculaire, hypokaliémie aiguë, et hyperthyroïdie, est une cause de paralysie périodique hypokaliémique. À notre connaissance, le déclenchement d'un accès de PPT, non diagnostiquée jusque là, par des bronchodilatateurs β_2 adrénergiques n'avait jamais été signalé auparavant. Il sera question, dans le présent article, du cas de deux jeunes hommes examinés au service des urgences pour un accès soudain de paralysie musculaire après l'administration de bronchodilatateurs β_2 adrénergiques en aérosol pour de l'asthme. Dans les deux cas, l'examen physique avait mis en évidence une hypertrophie de la glande thyroïde et une paralysie flasque symétrique, accompagnée d'une aréflexie des membres inférieurs. Les examens de laboratoire ont révélé une hypokaliémie, accompagnée d'une faible excrétion urinaire de K^+, mais un équilibre acido-basique sanguin normal, ce qui est l'indice d'un passage intracellulaire de K^+; la force musculaire est revenue chez les deux patients une fois que les taux sériques de K^+ eurent atteint 3.0 et 3.3 mmol/L. Une hyperkaliémie s'est produite chez l'un des patients après une recharge totale de chlorure de potassium de 110 mmol. Dans les deux cas, l'épreuve fonctionnelle thyroïdienne a donné des résultats qui ont permis d'établir le diagnostic d'hyperthyroïdie primitive, attribuable à la maladie de Basedow. Aussi, à la suite des deux exposés de cas, faudrait-il considérer les bronchodilatateurs β_2 adrénergiques comme de possibles facteurs déclenchants de PPT.

Keywords: β_2-adrenergic bronchodilator, hyperthyroidism, hypokalemia, paralysis, periodic paralysis

Periodic paralyses, including hypokalemic periodic paralysis, hyperkalemic periodic paralysis, and Andersen-Tawil syndrome, are caused by ion channelopathies of skeletal muscle and typically present in the first or second decade of life.[1] Hyperkalemic periodic paralysis is characterized by muscle weakness and a normal or slightly elevated serum potassium (K^+) level.

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Andersen-Tawil syndrome is characterized by episodic weakness, arrhythmias, and dysmorphic facial and skeletal features. Hypokalemic periodic paralysis is the most common form of periodic paralysis and is characterized by attacks of muscle paralysis associated with a low serum K^+ level due to an acute intracellular shifting.[2] The etiologies of hypokalemic periodic paralysis include familial periodic paralysis, thyrotoxic periodic paralysis (TPP), and sporadic periodic paralysis. Familial periodic paralysis is more common in whites and TPP or sporadic periodic paralysis in those of Asian extraction.[3] Possible mechanisms for hypokalemia in TPP include activation of the Na^+,K^+-ATPase pump by thyroid hormone, a hyperadrenergic state, and hyperinsulinemia in combination with reduced K^+ efflux into the skeletal muscle.[4–7]

Several factors have been reported to increase Na^+,K^+-ATPase activity and potentially precipitate an attack of TPP, including a high-carbohydrate diet and strenuous exercise (Table 1).[3,8–10] The triggering of an attack of undiagnosed TPP by β_2-adrenergic bronchodilators has, to our knowledge, not been reported previously. We describe two young men who presented to the emergency department (ED) with the sudden onset of muscle paralysis after administration of inhaled β_2-adrenergic bronchodilators for asthma.

CASE REPORTS

Case 1

A 24-year-old Chinese man presented to the ED with the sudden onset of bilateral leg paralysis. Three hours earlier, at a local district hospital, he had been administered nebulization of a β_2-adrenergic bronchodilator (salbutamol 5 mg) for asthma. He denied the use of diuretics or laxatives and had no family history of muscle paralysis or hyperthyroidism.

Table 1. Potential precipitants of thyrotoxic periodic paralysis

Trauma
Infection
Emotional stress
Exposure to cold
Strenuous exercise
Alcohol ingestion
High carbohydrate ingestion
Drugs
Corticosteroids
Epinephrine
Radioiodine therapy
Nonsteroidal antiinflammatory drugs
β_2-Adrenergic bronchodilators

On physical examination, his blood pressure was 174/60 mm Hg, pulse rate was 108 beats/min, respiratory rate was 16 breaths/min, and temperature was 36.9°C (98.4°F). There was no exophthalmos; however, his thyroid gland was mildly enlarged. A neurologic examination revealed symmetrical areflexia and complete paralysis of the lower extremities. The remainder of the physical examination was unremarkable.

The patient's laboratory investigations are shown in Table 2. Marked hypokalemia (K^+ 1.8 mmol/L) with a low urine K^+ excretion and a urine K^+/Cr ratio were the major abnormalities. Electrocardiography (ECG) revealed tachycardia, a left ventricular hypertrophy (LVH) pattern, and prominent U waves. After a total K^+ supplementation of 110 mmol (rate 10–20 mmol/h), his muscle strength had returned to normal, and his serum K^+ concentration was 3.0 mmol/L 6 hours after presentation. However, on repeat testing 6 hours later, he developed hyperkalemia (6.2 mmol/L), which returned to normal 4 hours later.

Thyroid function studies indicated a low thyroid-stimulating hormone (TSH), a high free thyroxine level, and a high level of TSH receptor antibodies. This patient was diagnosed with Graves disease and was commenced on carbimazole 10 mg three times daily orally. Inhaled ipratropium bromide was given to control his asthma. His hyperthyroidism was controlled,

Table 2. Laboratory results

Item	Normal range	Case 1	Case 2
Na^+	136–145 mmol/L	142	140
K^+	3.5–5.1 mmol/L	1.8*	2.1*
Cl^-	98–107 mmol/L	107	107
HCO_3^-	23–25 mmol/L	23.3	24.1
Urea (BUN)	2.9–8.9 mmol/L	7.2	3.2
Creatinine (Cr)	44–80 µmol/L	42	52
TSH	0.25–5.0 µIU/mL	< 0.03*	< 0.03*
Free T_4	0.8–2.0 ng/dL	3.2*	2.8*
Urine			
K^+ (mmol/L)		9.5	6.2
K^+/Cr (mmol/mmol)		1.4*	1.3*
TTKG		2.1*	2.7*

BUN = blood urea nitrogen; T_4 = thyroxine; TSH = thyroid-stimulating hormone; TTKG = transtubular K^+ gradient (a value < 3 suggests low K^+ excretion). TTKG = (urine K^+/serum K^+) ÷ (urine osmolality/serum osmolality)
*An abnormal value.

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and he reported no recurrence of muscle weakness in the following 4 months.

Case 2

A 22-year-old Chinese man presented with sudden muscle paralysis and inability to ambulate 2 hours after a bronchodilator inhalation (fenoterol hydrobromide 200 μg) for an asthma attack. He denied nausea, vomiting, diarrhea, or the use of diuretics, laxatives, or illicit drugs. His mother had hyperthyroidism. His blood pressure was 146/76 mm Hg, heart rate was 112 beats/min, respiratory rate was 18 breaths/min, and temperature was 36.8°C (98.2°F). His thyroid gland was enlarged. Muscle strength and reflexes were diminished in both lower extremities, and the rest of his physical examination was unremarkable.

The patient's laboratory investigations are shown in Table 2. His findings were similar to the first case above and included severe hypokalemia (2.1 mmol/L). An ECG revealed sinus tachycardia and U waves. After the administration of 30 mmol potassium chloride, his muscle strength recovered at a serum K^+ level of 3.3 mmol/L 4 hours after presentation. He was diagnosed with Graves disease and treated with oral propylthiouracil 50 mg three times daily and inhaled ipratropium bromide for asthma. He reported no recurrent muscle paralysis over the 6 months following his presentation.

DISCUSSION

We report two cases of young men without clinical features of hyperthyroidism who developed TPP shortly after β_2-adrenergic treatment for asthma. In neither case did we identify any other factors that could have induced acute intracellular shifting of K^+. It is likely that in both cases, β_2-adrenergic bronchodilators provoked TPP in the setting of a pre-existing predisposition to hypokalemia as a result of untreated thyrotoxicosis. This suggestion is supported by evidence that β_2-adrenergic agonists can significantly enhance Na^+,K^+-ATPase activity, thus inducing hypokalemia.[11,12] In addition, increased β_2-adrenergic activity has been shown to reduce K^+ efflux via inward rectifying K^+ channels, worsening the severity of hypokalemia.[13] Both patients developed TPP within the half-lives of the involved drugs (salbutamol 5–6 hours, fenoterol hydrobromide 1.7–2.3 hours). To our knowledge, these are the first reported cases of TPP triggered by administration of inhaled β_2-adrenergic bronchodilators.

Acute symmetrical paralysis is an uncommon ED complaint that can pose diagnostic challenges. The differential diagnosis includes brainstem stroke, myasthenic crisis, acute myelopathy, Guillain-Barré syndrome, tick paralysis, and botulism (Table 3). Our patients' presentation of acute paralysis with hypokalemia followed by rapid recovery after K^+ correction, coupled with the absence of bulbar and extraocular muscle involvement, paresthesias, or cranial neuropathies, is suggestive of hypokalemic periodic paralysis. Hypokalemic periodic paralysis can be caused by familial periodic paralysis, TPP, or sporadic periodic paralysis. Familial and sporadic periodic paralyses are characterized by an age at onset under 20 years and episodic muscle weakness, accompanied by a decrease in serum K^+ levels. Familial periodic paralysis is an autosomal dominant disorder, in contrast to sporadic periodic paralysis, for which the pathophysiology remains unclear.[14] TPP is classically characterized by a triad of muscle paralysis, acute hypokalemia, and hyperthyroidism and typically occurs in men between the ages of 20 and 40 years.[3]

Patients with TPP frequently do not have obvious symptoms of thyrotoxicosis such as hyperactivity, weight loss, heat intolerance, palpitations, increased appetite, or diaphoresis.[3] Because thyroid function tests are usually not immediately available in the ED, the diagnosis of TPP relies on clinical suspicion in the setting of clues such as young Asian adult males without a family history of periodic paralysis, ECG findings (tachycardia, atrioventricular block, LVH pattern), hypokalemia with a low K^+ excretion, normal acid-base status, hypocreatininemia, hypophosphatemia, and hypercalciuria.[3,15]

The therapeutic goal of emergency therapy for TPP is normalization of the serum K^+ concentration, not correcting a K^+ deficit. Because of this, the rate of potassium chloride supplementation should be kept low (< 10 mmol/h) to avoid rebound hyperkalemia on recovery unless life-threatening arrhythmias or impending respiratory failure is present. Nonselective β-blockers are an alternate therapy for the rapid termination of paralysis and have a role in helping avoid future attacks of TPP.[16] Definitive therapy of TPP involves restoration of a euthyroid state using antithyroid drugs, radioiodine, or thyroidectomy. When treating TPP in patients with coexisting asthma, the possibility of developing hypokalemia-induced complications during the attack and preventing the

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Table 3. Differential diagnosis of acute symmetrical paralysis[22–24]

Disorder	Associated conditions	Motor findings	Sensory findings	Other findings
Brainstem stroke (bilateral lesions or lower medulla lesion)	Hypertension, atrial fibrillation, diabetes	Rapid onset of quadriparesis to quadriplegia	Depending on the areas involved	Altered mental status, cranial neuropathy, bulbar signs, cerebellar signs, autonomic dysfunction
Acute myelopathy	Trauma; autoimmune, infectious, neoplastic, vascular diseases	Loss of motor function caudal to the level of the injury	Loss of sensory function caudal to the level of the injury	Absent bowel and bladder control
Myasthenic crisis	Myasthenia gravis	From fluctuating degrees of weakness that worsens with use to generalized weakness	Absent	Respiratory arrest Bulbar weakness
Guillain-Barré syndrome	A preceding gastrointestinal or upper respiratory tract infection	Progressive ascending weakness	Frequently a prodrome of sensory impairment	Cranial neuropathy Areflexia Rare dilated pupils
Tick paralysis	Presence of a tick or tick crater	Progressive ascending weakness	Generally absent	Respiratory impairment Rare dilated pupils
Botulism	A prodrome of gastrointestinal symptoms	Progressive descending weakness	Absent	Symmetrical cranial neuropathy, dilated pupils
Periodic paralysis	Onset at the first or second decade	Rapid onset of generalized or focal muscle weakness	Absent	Variable serum K^+ level during attacks, hyperthyroidism in TPP

TPP = thyrotoxic periodic paralysis.

recurrence of both TPP and asthma in chronic therapy must be balanced. As illustrated in one of the two patients we describe, potassium chloride supplementation may be warranted and when administered should be at a low rate. The administration of nonselective β-blockers should be performed only in a monitored setting and on patients with very mild asthma.[13] In chronic asthma therapy, caution in the use of β_2-adrenergic bronchodilators and systemic steroids is warranted as both can induce TPP.[17–21] Early recognition of TPP and prompt management avoid life-threatening complications such as respiratory failure and arrhythmias.

CONCLUSION

We describe two young asthmatic men who developed TPP shortly after the inhalation of β_2-adrenergic bronchodilators. In patients with symmetrical paralysis, hypokalemic periodic paralysis should be considered. Furthermore, in patients diagnosed with hypokalemic periodic paralysis, the possibility of TPP should be investigated through thyroid function tests. Our cases demonstrate that β_2-adrenergic bronchodilators should be considered a potential precipitant of TPP.

Competing interests: None declared.

REFERENCES

1. Raja Rayan DL, Hanna MG. Skeletal muscle channelopathies: nondystrophic myotonias and periodic paralysis. *Curr Opin Neurol* 2010;23:466-76, doi:10.1097/WCO.0b013e32833cc97e.
2. Lin SH, Davids MR, Halperin ML. Hypokalaemia and paralysis. *QJM* 2003;96:161-9, doi:10.1093/qjmed/hcg021.
3. Lin SH. Thyrotoxic periodic paralysis. *Mayo Clin Proc* 2005;80:99-105.
4. Maciel RM, Lindsey SC, Dias da Silva MR. Novel etiopathophysiological aspects of thyrotoxic periodic paralysis. *Nat Rev Endocrinol* 2011;7:657-67, doi:10.1038/nrendo.2011.58.
5. Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta2-receptor stimulation by circulating epinephrine. *N Engl J Med* 1983;309:1414-9, doi:10.1056/NEJM198312083092303.
6. Ryan DP, da Silva MR, Soong TW, et al. Mutations in potassium channel Kir2.6 cause susceptibility to thyrotoxic hypokalemic periodic paralysis. *Cell* 2010;140:88-98, doi:10.1016/j.cell.2009.12.024.
7. Cheng CJ, Lin SH, Lo YF, et al. Identification and functional characterization of Kir2.6 mutations associated with non-familial hypokalemic periodic paralysis. *J Biol Chem* 2011;286:27425-35, doi:10.1074/jbc.M111.249656.
8. El-Hennawy AS, Nesa M, Mahmood AK. Thyrotoxic hypokalemic periodic paralysis triggered by high carbohydrate diet. *Am J Ther* 2007;14:499-501, doi:10.1097/MJT.0b013e31814daf53.
9. Akar S, Comlekci A, Birlik M, et al. Thyrotoxic periodic paralysis in a Turkish male; the recurrence of the attack after radioiodine treatment. *Endocr J* 2005;52:149-51, doi:10.1507/endocrj.52.149.

10. Aldemir M, Güloğlu C, Balakan O, et al. Thyrotoxic periodic paralysis: a case report and review of the literature. *Eur J Gen Med* 2004;1:48-51.
11. Moratinos J, Reverte M. Effects of catecholamines on plasma potassium: the role of alpha- and beta-adrenoceptors. *Fundam Clin Pharmacol* 1993;7:143-53, doi:10.1111/j.1472-8206.1993.tb00228.x.
12. Haffner CA, Kendall MJ. Metabolic effects of beta 2-agonists. *J Clin Pharm Ther* 1992;17:155-64, doi:10.1111/j.1365-2710.1992.tb01285.x.
13. Ruff RL. Insulin acts in hypokalemic periodic paralysis by reducing inward rectifier K^+ current. *Neurology* 1999;53:1556-63, doi:10.1212/WNL.53.7.1556.
14. Sung CC, Cheng CJ, Lo YF, et al. Genotype and phenotype analysis of patients with sporadic periodic paralysis. *Am J Med Sci* 2012;343:281-5.
15. Barahona MJ, Vinagre I, Sojo L, et al. Thyrotoxic periodic paralysis: a case report and literature review. *Clin Med Res* 2009;7:96-8, doi:10.3121/cmr.2009.816.
16. Lin SH, Lin YF. Propranolol rapidly reverses paralysis, hypokalemia, and hypophosphatemia in thyrotoxic periodic paralysis. *Am J Kidney Dis* 2001;37:620-3, doi:10.1053/ajkd.2001.22090.
17. Ober KP. Thyrotoxic periodic paralysis in the United States. Report of 7 cases and review of the literature. *Medicine* 1992;71:109-20, doi:10.1097/00005792-199205000-00001.
18. Liu Z, Braverman LE, Malabanan A. Thyrotoxic periodic paralysis in a Hispanic man after the administration of prednisone. *Endocr Pract* 2006;12:427-31, doi:10.4158/EP.12.4.427.
19. Miyashita Y, Monden T, Yamamoto K, et al. Ventricular fibrillation due to severe hypokalemia induced by steroid treatment in a patient with thyrotoxic periodic paralysis. *Intern Med* 2006;45:11-3, doi:10.2169/internalmedicine.45.1495.
20. Wongraoprasert S, Buranasupkajorn P, Sridama V, et al. Thyrotoxic periodic paralysis induced by pulse methylprednisolone. *Intern Med* 2007;46:1431-3, doi:10.2169/internalmedicine.46.0044.
21. Tessier JJ, Neu SK, Horning KK. Thyrotoxic periodic paralysis (TPP) in a 28-year-old Sudanese man started on prednisone. *J Am Board Fam Med* 2010;23:551-4, doi:10.3122/jabfm.2010.04.090220.
22. Chaudhuri A, Behan PO. Myasthenic crisis. *QJM* 2009;102:97-107, doi:10.1093/qjmed/hcn152.
23. McGillicuddy DC, Walker O, Shapiro NI, et al. Guillain-Barre syndrome in the emergency department. *Ann Emerg Med* 2006;47:390-3, doi:10.1016/j.annemergmed.2005.05.008.
24. Edlow JA, McGillicuddy DC. Tick paralysis. *Infect Dis Clin North Am* 2008;22:397-413, doi:10.1016/j.idc.2008.03.005.

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