

Conn's Syndrome, Subclinical Cushing's Syndrome and Thyrotoxicosis Presenting as Hypokalemic Periodic Paralysis: A Case Report

Hipokalemik Periyodik Paralizi ile Seyreden Conn, Subklinik Cushing ve Tirotoksikoz Olgusu

İnan Anaforoğlu, Alimdar Şimşek*, Ekrem Algün

Trabzon Numune Training and Research Hospital, Department of Endocrinology and Metabolism, Trabzon, Turkey

*Trabzon Numune Training and Research Hospital, Department of Radiology, Trabzon, Turkey

Abstract

Thyrotoxicosis and primary hyperaldosteronism both cause hypokalemic periodic paralysis. Here we report a 51-year-old woman presenting with severe hypokalemia due to both thyrotoxicosis and primary hyperaldosteronism. At first presentation, she had a potassium level of 1.5 mEq/L and thyrotoxicosis due to a hot nodule, and was diagnosed as having thyrotoxic hypokalemic periodic paralysis. After treatment with propylthiouracil and potassium, she completely regained muscle strength. Nevertheless, a decrease in potassium level was observed again when the replacement of potassium was discontinued. The further diagnostic work-up of the patient, who had also history of hypertension, revealed primary hyperaldosteronism and subclinical Cushing's syndrome due to adrenal adenoma on the left side. Whether thyrotoxicosis contributed to the hypokalemic periodic paralysis in this patient is a matter of debate. Adrenal hyperfunction should be considered in all patients with hypertension and hypokalemia regardless of the presentation of the case. *Türk Jem 2009; 13: 87-90*

Key words: Hypokalemic periodic paralysis, thyrotoxicosis, hyperaldosteronism, Subclinical Cushing's syndrome

Özet

Hem tirotoksikoz hem de hiperaldosteronizm hipokalemik periyodik paraliziye neden olabilen tablolardır. Biz burada, primer hiperaldosteronizmle birlikte tirotoksikozun da olduğu ciddi hipokalemi ile gelen 51 yaşındaki olguyu sunacağız. Hastanın gelişinde 1,5 mEq/L düzeyinde hipokalemi, alt ekstremitelerde paralizisi ve sıcak tiroid nodülüne bağlı tirotoksikozu tespit edildi; tirotoksikoza bağlı hipokalemik periyodik paralizisi olduğu düşünüldü. Propiltiourasil ve potasyum replasmanı sonrası hastanın paralizisi tamamen düzeldi, ancak potasyum replasmanı kesildikten sonra hastanın hipokalemi devam etti. Hipertansiyon öyküsü de olan hastanın yapılan tetkikleri sonucunda hiperaldosteronizmi, Subklinik Cushing sendromu ve solda sürrenal adenomu tespit edildi. Tirotoksikozun bu hastadaki hipokalemik periyodik paralizi tablosuna katkısı tartışılabilir, ancak hipertansiyon ve hipokalemi olan her hasta adrenal fonksiyonlar yönünden araştırılmalıdır. *Türk Jem 2009; 13: 87-90*

Anahtar kelimeler: Hipokalemik periyodik paralizi, tirotoksikoz, hiperaldosteronizm, Subklinik Cushing sendromu

Introduction

Thyrotoxic hypokalemic periodic paralysis, characterized by acute systemic weakness and low serum potassium, is the most common form of acquired periodic paralysis (1,2). It is typically seen in Asian populations and may be seen in Caucasian and Turkish populations (3). Primary hyperaldosteronism or Conn's syndrome is another endocrinopathy causing hypokalemic periodic paralysis (4,5). Patients are typically admitted to emergency units

with recurrent episodes of muscle weakness lasting minutes to days. The weakness initially involves the legs, but may eventually spread to the arms, and it may progress to a generalized flaccid paralysis (1,2). The most consistent laboratory finding is low serum potassium concentration, less than 3.5 mmol/L, and much lower in most cases. Serum potassium concentrations are consistently normal between attacks, and occasional patients may be normokalemic during an attack (2). Increased adrenergic activity by thyrotoxicosis and an assumed genetic predisposition result in

Address for Correspondence: İnan Anaforoğlu, MD, Trabzon Numune Training and Research Hospital, Department of Endocrinology and Metabolism, Trabzon, Turkey
E-mail: inanaforoglu@hotmail.com **Received:** 05.01.2010 **Accepted:** 26.01.2010

Turkish Journal of Endocrinology and Metabolism, published by Galenos Publishing. All rights reserved.

increased $\text{Na}^{+}\text{-K}^{+}$ ATPase activity with increased intracellular transport of potassium. Hypokalemia in this disorder does not reflect the total body potassium deficit, but rather a shift of potassium from the extracellular to the intracellular space, and rebound hyperkalemia during recovery has been reported. A high carbohydrate meal with increased insulin secretion, glycogen deposition, vigorous exercise, high salt intake, or the normal nocturnal potassium flux then drives serum potassium levels even lower, resulting in flaccid neuromuscular paralysis (2). Recovery is rapid with appropriate treatment. After restoration of normal thyroid function, the paralysis does not occur. In patients with primary hyperaldosteronism, surgical removal of the aldosterone-producing adenoma is recommended. If surgery cannot be performed, or in cases of bilateral adrenal hyperplasia, medication that blocks the actions of aldosterone is the choice for treatment (5). The two other major causes of hypertension and hypokalemia are renovascular disease and diuretic therapy, which may be surreptitious. Less common causes include Cushing's syndrome, licorice ingestion, certain forms of congenital adrenal hyperplasia, Liddle's syndrome, rare renin-secreting tumors and ion channel mutations. Herein, we present a case of a middle-aged woman with thyrotoxic hypokalemic periodic paralysis on admission. Although her paralysis improved with treatment, hypokalemia persisted. She was evaluated for hypokalemia concomitant with hypertension and the diagnosis of primary hyperaldosteronism and subclinical Cushing's syndrome was established.

Case Report

A 51-year-old woman with leg weakness was admitted to the emergency unit. She had experienced 3 episodes of transient muscle weakness in her legs over the past 1.5 years. Her medical history included hypertension for approximately 10 years. She was on multiple antihypertensive drugs, including losartan potassium 100 mg/day, amlodipine 10 mg/day, doxazosin mesylate 4 mg/day, metoprolol 100 mg/day, and hydrochlorothiazide 25 mg/day. On admission, her blood pressure was 160/80 mm Hg, and the pulse rate was 78 beats/min. Her height was 163 cm, and weight was 70 kg. There were no Cushingoid features. On physical examination, a 3 cm nodule was palpated in the left anterior neck. Symmetrically decreased strength in both lower extremities (2/5) with normal results of a sensory examination was observed. Deep tendon reflexes were diminished in the lower extremities.

The initial laboratory findings were noteworthy with potassium level of 1.5 mEq/L and sodium level of 148 mmol/L. Biochemical analysis and blood counts were normal. Thyroid function tests were compatible with primary hyperthyroidism: triiodothyronine (T3) of 5.86 pg/mL (normal range, 1.8-4.6 pg/mL); thyroxine (T4) of 1.96 ng/dL (normal range, 0.9-1.7 ng/dL); and thyrotropin of 0.005 uIU/mL (normal range, 1.27-4.2 uIU/mL). She was referred to endocrinology clinic and hospitalized. Her family history included no thyroid disease or periodic paralysis. Thyroid ultrasonography demonstrated a nodular lesion with cystic changes, measuring 15.2x12.2 mm (Figure 1). On thyroid scanning, accumulation in the left lobe compatible with a hot nodule and suppression in the other thyroid area were detected. The patient was prescribed propylthiouracil to control her thyrotoxicosis; she was already taking a beta-blocker. The patient's potassium was replaced. She responded well to the treatment and completely regained muscle

strength. The diagnosis of thyrotoxic hypokalemic periodic paralysis was presumed. Nevertheless, a decrease in potassium level was observed each time immediately after the replacement of potassium was stopped, without signs of muscle weakness. The possible mechanisms of hypertension and hypokalemia in this patient were sought. The family history was non-contributory. Primary hyperaldosteronism was suggested. Among the antihypertensive medications the patient was taking, losartan potassium, metoprolol, and hydrochlorothiazide were discontinued because of their potential effect on measurements of aldosterone, renin and catecholamines. Amlodipine was increased to 20 mg/day, and doxazosin mesylate was increased to 8 mg/day. She was given oral potassium chloride. A normokalemic state was obtained with oral medication. The patient was discharged and asked to come back after 3 weeks for new therapy. After achieving liberal sodium intake and normokalemia, plasma aldosterone and renin activities were measured. A high level of aldosterone of 51.6 ng/dL with suppressed renin of 0.2 ng/mL/h and a high ratio of aldosterone to renin (258) were compatible with the diagnosis of primary hyperaldosteronism. As a confirmatory test, a saline infusion test was applied. Plasma aldosterone was found to be 66.8 ng/dL after saline infusion test. To exclude Cushing's syndrome, the dexamethasone suppression test was performed. Morning cortisol level was not suppressed by pretreatment with 1 and 2 mg dexamethasone (2.5 and 5.85 µg/dL, respectively). The results of the high-dose dexamethasone suppression test (8 mg) supported the diagnosis of Cushing's syndrome. Plasma corticotropin level was 5.69 pg/mL. The tests were repeated after the patient was discharged from the hospital to exclude the contribution of hospital stress, and the results were consistent with Cushing's syndrome. Imaging of the adrenal glands by abdominal magnetic resonance imaging showed a left adrenal mass of 17x13 mm consistent with adenoma (Figure 2). The diagnosis of primary hyperaldosteronism and subclinical Cushing's syndrome was presumed. The patient declined to undergo adrenal venous sampling or surgery. Spironolactone, 200 mg/day, was started gradually. In the second week of therapy, the patient became normokalemic without support of oral potassium perchloride. An antihypertensive regimen composed of spironolactone 200 mg/day and losartan 50 mg/day was sufficient to control her blood pressure. Meanwhile, after euthyroidism was achieved with antithyroid medication, the patient was given radioactive iodine treatment. She is on the thirteenth month of radioactive therapy,



Figure 1. Thyroid ultrasonography

and is still euthyroid. Her hypercorticism was consistent with the criteria of subclinical Cushing's syndrome. The results of a bone mineral density test, a 75 g oral glucose tolerance test, and her lipid parameters were normal. Except for hypertension and intermittent paralysis due to hypokalemia, there were no typical features of primary aldosteronism and Cushing's syndrome.

Discussion

Thyrotoxicosis and primary hyperaldosteronism both cause hypokalemic periodic paralysis. Thyrotoxic periodic paralysis is usually associated with Graves' disease (2). Rare cases of thyrotoxic periodic paralysis due to toxic adenoma have been reported as well (6-9). Thyroiditis, toxic nodular goiter, thyrotropin-secreting pituitary tumor, ingestion of thyroxine, silent thyroiditis, and therapeutic doses of iodine are other reported causes of thyrotoxic hypokalemic periodic paralysis (3,10-12). The reported case had toxic nodular goiter. In a survey analyzing cases from Turkey, the major etiological factor was Graves' disease (73.7%). Toxic nodular goiter was the second most common cause (18.4%), consisting of four toxic adenomas and three toxic multinodular goiters (3). The relatively high incidence, different from the previous reports, was attributed to iodine deficiency and the high prevalence of toxic nodular goiter in Turkey (3). This patient had both thyrotoxicosis and primary hyperaldosteronism. As far as we know, only two similar cases have been reported to date (13, 14). Whether thyrotoxicosis or hyperaldosteronism triggered hypokalemic periodic paralysis in this patient is a matter of debate. However, considering that she had a history of hypertension for 10 years without any paralytic attacks, except for the last 1.5 years, and no evidence or sign of thyrotoxicosis, we can propose that hyperaldosteronism is likely to be the etiological factor in hypokalemic periodic paralysis in this patient. It is well known that the clinical and biochemical spectrum of primary hyperaldosteronism may vary. Hypokalemia may be absent; however, in most patients, hypokalemia may become evident with addition of a potassium-wasting diuretic (e.g. hydrochlorothiazide, furosemide) (15). Our patient has been using hydrochlorothiazide for 2 years, and the paralytic attacks have occurred during the last 1.5 years. There is a possible link between

diuretic use and hypokalemic periodic paralytic attacks, which may be triggered by thyrotoxicosis. Clinicians should keep primary hyperaldosteronism in mind in patients with hypokalemia caused by diuretics (15). The Endocrine Society has recently identified other situations in patients that warrant an evaluation for primary hyperaldosteronism, including stage 2 or 3 hypertension, drug-resistant hypertension, hypertension and spontaneous or diuretic-induced hypokalemia, hypertension with adrenal incidentaloma, or hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (40 years or younger), or first-degree relatives of patients with primary hyperaldosteronism and hypertension (15). The two other major causes of hypertension and hypokalemia are renovascular disease (in which hypersecretion of renin leads sequentially to increased angiotensin II and aldosterone secretion) and diuretic therapy, which may be surreptitious. Less common causes include Cushing's syndrome, licorice ingestion, certain forms of congenital adrenal hyperplasia, Liddle's syndrome, rare renin-secreting tumors and channelopathies. Cushing's syndrome may lead to hypokalemia due in part to the overproduction of corticotropin-dependent compounds such as deoxycorticosterone, corticosterone, and cortisol. In our patient, the hypercortisolemic state was not related to corticotropin oversecretion (16). Subclinical Cushing's syndrome with mild hypercortisolism, but without clinical manifestations of Cushing's syndrome, is the most frequent (5-8%) hormonal abnormality detected in patients with adrenal incidentalomas (17). Subclinical Cushing's syndrome may be related to the components of metabolic syndrome, as well as to metabolic syndrome itself and osteoporosis (18,19). However, our patient's bone mineral density was normal, and she had only hypertension among the components of metabolic syndrome.

Although it is rare in non-Asians, hypokalemic periodic paralysis can be seen in these populations. As in our case, diagnosis may be delayed. However, early diagnosis may prevent serious complications.

The present case is uncommon. Two cases of thyrotoxicosis and primary aldosteronism complicating hypokalemic periodic paralysis have been published in the literature to date (13,14). There are some subclinical cases of Cushing's syndrome concomitant with primary hyperaldosteronism that have been identified. Clinicians should consider that subclinical Cushing's syndrome, as in this situation, is not very rare (20-22). In conclusion, adrenal function should be assessed in a patient with hypertension and hypokalemia, regardless of the presentation.

References

- Bergeron L, Sternbach GL. Thyrotoxic periodic paralysis. *Ann Emerg Med* 1988; 17: 843-845.
- Ahluwat SK, Sachdev A. Hypokalaemic paralysis. *Postgrad Med J* 1999; 75: 193-197.
- Cesur M, Bayram F, Temel AM, Ozkaya M, Kocer A, Ertorer ME, Koc F, Kaya A, Gullu S. Thyrotoxic hypokalemic periodic paralysis in a Turkish population: three new case reports and analysis of the case series. *Clin Endocrinol (Oxf)* 2008; 68: 143-152.
- Conn JW, Knopf RF, Nesbit RM. Clinical characteristics of primary aldosteronism from an analysis of 145 cases. *Am J Surg* 1964; 107: 159-172.
- Ma JT, Wang C, Lam KS, Yeung RT, Chan FL, Cheung PS, Coghlan JP, Scoggins BA, Stockigt JR. Fifty cases of primary hyperaldosteronism in Hong Kong Chinese with a high frequency of periodic paralysis. Evaluation of techniques of tumor localization. *Q J Med* 1986; 61: 1021-1037.
- Kelley DE, Gharib H, Kennedy FP, Duda RJ, McManis MB. Thyrotoxic periodic paralysis. Report of 10 cases and review of electromyographic findings. *Arch Intern Med*. 1989; 149: 2597-2600.



Figure 2. Imaging of adrenal gland

7. Norris FH Jr, Clark EC, Biglieri EG. Studies in thyrotoxic periodic paralysis. Metabolic and ultrastructural studies. *J Neurol Sci* 1971; 13: 431-432.
8. Tagami T, Usui T, Shimatsu A, Naruse M. Toxic thyroid adenoma presenting as hypokalemic periodic paralysis. *Endocr J* 2007; 54: 797-803.
9. Ozaki H, Mori K, Nakagawa Y, Hoshikawa S, Ito S, Yoshida K. Autonomously functioning thyroid nodule associated with thyrotoxic periodic paralysis. *Endocr J* 2008; 55: 113-119.
10. Kung AW. Clinical Review: Thyrotoxic Periodic Paralysis: A Diagnostic Challenge. *J Clin Endocrinol Metab* 2006; 91: 2490-2495.
11. Kao CL, Tu ST, Su SL. Thyrotoxic periodic paralysis: analysis of 13 cases. *J Int Med Taiwan* 2002; 13: 22-26.
12. Nakamura S, Sugimoto M., Kosaka J, Watanabe H, Shima H, Kawahira S (1990) *Jpn J Med* 29:623-627.
13. Yokota N, Uchida T, Sasaki A, Kobayashi K, Kida O, Yamamoto Y, Eto T, Tanaka K. Silent thyroiditis with thyroid-stimulation blocking antibodies (TSBAbs). *Jpn J Med* 1991; 30: 219-223.
14. Hamaguchi K, Sakai F, Ishihara N, Ebata K, Nakagawa S. Quadriparesis in primary aldosteronism: Hypokalemic necrotizing myopathy. [in Japanese]. *Rinsho Shinkeigaku* 1973; 13: 705-710.
15. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr, Montori VM, Endocrine Society. Case Detection, Diagnosis, and Treatment of Patients with Primary Aldosteronism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2008; 93: 3266-3281.
16. Stewart MP. Williams textbook of endocrinology. (Ed: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR) Philadelphia, Saunders/Elsevier, 2008, 445-541.
17. Reincke M. Subclinical Cushing's syndrome. *Endocrinol Metab Clin North Am* 2000; 29: 43-56.
18. Terzolo M, Pia A, Osella G, Reimondo G, Bovio S, Daffara F, Procopio M, Paccotti. Adrenal incidentaloma: a new cause of the metabolic syndrome? *J Clin Endocrinol Metab* 2002; 87: 998-1003.
19. Chiodini I, Torlontana M, Carnevale V, Guglielmi G, Cammisia M, Trischitta V, Scillitani A. Bone loss rate in adrenal incidentalomas: a longitudinal study. *J Clin Endocrinol Metab* 2001; 86: 5337-5341.
20. Adachi J, Hirai Y, Terui K, Nakano T, Fukuda Y, Suda T, Sasano H. A report of 7 cases of adrenal tumors secreting both cortisol and aldosterone. *Intern Med* 2003; 42: 714-718.
21. Okura T, Miyoshi K, Watanabe S, Kurata M, Irita J, Manabe S, Fukuoka T, Higaki J, Sasano H. Coexistence of three distinct adrenal tumors in the same adrenal gland in a patient with primary aldosteronism and preclinical Cushing's syndrome. *Clin Exp Nephrol* 2006; 10: 127-130.
22. Kurtulmus N, Yarman S, Azizlerli H, Kapran Y. Co-secretion of aldosterone and cortisol by an adrenocortical carcinoma. *Horm Res* 2004; 62: 67-70.