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NOTE

Hypokalemic Periodic Paralysis Associated with Thyrotoxicosis, Renal Tubular Acidosis and Nephrogenic Diabetes Insipidus

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Abstract. A 19-year-old girl presented at our emergency room with hypokalemic periodic paralysis. She had a thyrotoxic goiter and had experienced three paralytic attacks during the previous 2 years on occasions when she stopped taking antithyroid drugs. In addition to thyrotoxic periodic paralysis (TPP), she had metabolic acidosis, urinary potassium loss, polyuria and polydipsia. Her reduced ability to acidify urine during spontaneous metabolic acidosis was confirmed by detection of coexisting distal renal tubular acidosis (RTA). The polyuria and polydipsia were caused by nephrogenic diabetes insipidus, which was diagnosed using the water deprivation test and vasopressin administration. Her recurrent and frequent paralytic attacks may have been the combined effects of thyrotoxicosis and RTA. Although the paralytic attack did not recur after improving the thyroid function, mild acidosis and nephrogenic DI have been remained subsequently. Patients with TPP, especially females with atypical metabolic features, should be investigated for possible precipitating factors.

Key words: Hypokalemic periodic paralysis, Thyrotoxicosis, Renal tubular acidosis

THERE are only two previous reports of hypokalemic periodic paralysis caused by thyrotoxicosis and renal tubular acidosis (RTA) [1, 2]. We report a case of a 19-year-old Korean female with these coexisting conditions. Our patient did not have nephrocalcinosis, which is regarded as the cause of RTA, but was positive for anti-Ro antibodies and had nephrogenic diabetes insipidus (DI). During treatment, severe metabolic acidosis resolved as thyroid function improved, but mild metabolic acidosis and nephrogenic DI have been remained without paralytic attack subsequent 2 years.

Case Report

A 19-year-old female was admitted with paralysis of both lower extremities. She had been treated for Graves' disease and had experienced episodes of hypokalemic periodic paralysis when she had discontinued antithyroid drugs on three previous occasions. At the time of her admission, she had not taken her medication (propylthiouracil) for a week. On the night before admission, she took an exercise, and then at the 6 a.m. on the day of admission she again complained proximal muscle weakness.

On examination, she had paralysis of the lower legs and a non- tender goiter. No sensory deficit or respiratory or visual difficulties were detected. She did not have a family history of thyroid, neuromuscular or autoimmune disease.

Laboratory tests revealed the following serum metabolite levels: on the day of admission, sodium, 143 mEq/L; potassium, 2.3 mEq/L; creatinine, 0.6 mg/dL; chloride, 116 mEq/L; calcium, 10.5 mg/dL; and phosphorus, 3.4 mg/dL. Arterial pH varied from 7.29–7.305, PCO2 varied from 27.7–35.5 mmHg and bicarbonate level varied from 13–17.3 mmol/L. A thyroid function test showed a thyroid-stimulating hormone level of 0.012 IU/mL (normal = 0.4–4 IU/mL), a T3 level of 333 ng/dL (normal = 80–180 ng/dL) and a free T4 level of 3.45 ng/dL (normal = 0.8–1.87 ng/dL). She was positive for anti thyroglobulin antibody at a titer of 1:100, for anti microsomal antibody at a ti-

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Table 1A. Water deprivation test, aqueous vasopressin was injected after 7 h of water deprivation.

Time (h)	0	1	2	3	4	5	6	7	7.5	8	8.5
Serum osmolality (mOsmol/kg)	292	291	295	288	291	294	295	297	300	296	301
Urine osmolality (mOsmol/kg)	280	305	280	216	316	319	309	313	308	308	313

ter of 1:6,400 and strongly positive for TSH receptor autoantibody (TR Ab) at a level of 405 U/L (by RIA, RSR Ltd, Cardiff, UK, positive; >10 U/L). The patient was diagnosed with hypokalemic periodic paralysis and thyrotoxicosis and was treated with oral potassium replacement (24 mmol/d), propylthiouracil (300 mg/d) and propranolol (60 mg/d).

In addition to hypokalemic paralysis, she had metabolic acidosis. Therefore, we investigated the hypokalemia and metabolic acidosis. Arterial blood gas analysis showed normal anion-gap metabolic acidosis. Her 24 hour urine was collected from the admission day until next day during the paralysis. Urinary potassium excretion was 13.7 mEq/L, serum potassium level was 2.3 mEq/L and serum and urinary osmolality were 300 and 158 mOsm/kg respectively. Her transtubular potassium gradient was 11.3, indicating renal potassium loss. On 2nd hospital day, her arterial pH was 7.305 and her arterial bicarbonate level was 17.3 mmol/L, her urine pH was 8.0, which is indicative of an inability to decrease the pH of urine. In addition, the urinary sodium level was 35 mEq/L, the potassium level was 13.7 mEq/L and the urine chloride level was 33 mEq/L, thus the calculated urine anion gap was 15.7 suggested that her urinary NH_4^+ excretion was impaired. It was considered unnecessary to perform an ammonium chloride loading test because the patient had overt acidosis (plasma bicarbonate level <20 mEq/L) and a urinary pH >6.0. There was no aciduria or glucosuria, which ruled out other proximal tube defects. We confirmed the coexistence of distal RTA.

We then investigated the cause of the RTA. Plain abdominal radiography and abdominal sonography showed no evidence of nephrocalcinosis and urinary calcium excretion was 136.5 mg/d. A test for antinuclear antibody was positive at a titer of 1:80. The patient also tested positive for anti Ro antibody by ELISA (98.1 U/mL; normal, <20 U/mL). However, tests for anti-Smith antibody, anti-La antibody by ELISA, anti-ribonucleoprotein antibody and rheumatoid factor were all negative. Complement levels, including C3, C4 and CH50 levels, were normal. There were no symptoms of dry eyes or a dry mouth and she did not meet the criteria for Sjögren's syndrome.

Her paralytic attack had been lasted second hospital day, the patient complained of polyuria and polydipsia. On the second day of admission, she still had lower limb paralysis; her urine volume exceeded 3000 mL/d. Her urine osmolality was 158 mosm/kg and her serum osmolality was 300 mosm/kg. The patient recovered from paralysis wholly on the thrid hospital day with serum potassium levels was 3.0 mEq/L. Her paralysis had been lasted about 48 hours. After the paralytic attack recovered, we suspected DI and performed a water deprivation test on 20th hospital day. Urine osmolality did not increase and urinary volume did not decrease by 7 hour of water deprivation and were not altered by injection of vasopressin (Table1A). Therefore, we made a diagnosis of partial nephrogenic DI combined with RTA.

The metabolic acidosis persisted until the 15th day of hospitalization, at which time her arterial blood gas had normalized without alkaline therapy and she was discharged on the 24th day of hospitalization. One month later, her serum sodium level was 141 mEq/L and her potassium level was 4.0 mEq/L. She did not experience a hypokalemic paralytic attack during the subsequent 2 years. The lab data obtained at November 2009, 2 year after the paralytic episode, showed she still had mild metabolic acidosis. Her arterial pH was 7.364, bicarbonate level was 18.2 mmol/L and PCO2 was 32.7 mmHg, the urine gas performed same time, the urine pH was 6.925. However, the electrolytes were within normal range (Na 141 mEq/L, K 3.8 mEq/L, Cl 106 mEq/L). Water deprivation test was performed again and she still had nephrogenic DI (Table 1B).

Discussion

Hypokalemic periodic paralysis is caused by several heterogenous diseases, such as familial hypokalemic periodic paralysis, thyrotoxicosis and distal renal tubular acidosis [3]. Most cases of hypokalem-

Table 1B. Water deprivation test performed 2 years after paralytic attack. Aqueous vasopressin was injected after 4 h of water deprivation.

Time(hr)	0	1	2	3	4	4.5	5	5.5
Serum osmolality(mOsmol/kg)	289	287	286	297	299	313	315	297
Urine osmolality(mOsmol/Kg)	303	305	303	299	306	315	318	312

Table 2. Acid–base changes and thyroid function during hypokalemic periodic paralytic attacks over 2 years.

Date of attack (day/month/yr)	2/12/2005	03/03/2006	09/03/2007	30/05/2007
pH	7.442	n/d	7.367	7.29
HCO_3^+ (mmol/L)	22	n/d	17.3	13
K^+ (mEq/L)	2	2.4	2.5	2.3
Na^+(mEq/L)	141	142	142	143
Cl^-	107	110	117	116
T3 (ng/dL)	118	232.7	304	333
Free T4 (ng/dL)	1.18	2.63	3.19	3.45
TSH (μIU/mL)	0.007	0.01	0.005	0.012
AMA	1:400	1:25600	1:25600	1:6400
ATA	1:100	(-)	1:100	1:100
TR Ab (U/L)	37.71	22.63	66.8	405

AMA, antimicrosomal antibody; ATA, antithyroglobulin antibody; TRAb, TSH receptor autoantibody; n/d, not done.

ic periodic paralysis are caused by a single disease. However, in our patient, the frequent and repeated paralytic attacks were not only caused by thyrotoxicosis but also by distal RTA. Our patient experienced recurrent episodes of hypokalemic periodic paralysis when she developed thyrotoxicosis secondary to discontinuation of her antithyroid drug regimen. Thus, the hypokalemic paralytic attacks were regarded as thyrotoxic periodic paralysis (TPP). However, the patient had several features atypical of TPP. TPP occurs primarily in male Asians and has a male-to-female incidence of 20:1 [4]. The incidence is highest in patients aged 20–29 years. Our patient was a relatively young female; her first attack occurred at 18 years of age and she experienced four episodes during the subsequent 2 years (Table 2). In typical TPP, hypokalemia induces an influx of potassium into the cell but there is no renal potassium loss and no disturbance in acid–base balance [4]. In our patient, metabolic acidosis was coexistent with renal potassium loss. Further investigations into the causes of these effects are warranted.

Distal RTA, one of the causes of hypokalemic periodic paralysis, is characterized by an inability of the distal nephron to acidify the urine, which results in metabolic acidosis accompanied by hyperchloremia and a normal anion gap [5]. Cases of RTA-associated thyrotoxicosis have been reported previously [6, 7]. The mechanism underlying this association is unclear. In addition, hypokalemic periodic paralysis caused by two predisposing diseases occurs rarely. To our knowledge, only two cases have been reported in which hypokalemic periodic paralysis was caused by a combination of thyrotoxicosis and distal RTA. The first case involved a Mexican woman with TPP, RTA, nephrogenic DI and nephrocalcinosis [1]. In that case, RTA of unknown origin was considered to have induced nephrocalcinosis and nephrogenic DI, the hyperthyroidism appeared later. Our patient manifested the same characteristics, except for nephrocalcinosis. However, our patient first detected hyperthyroidism, and arterial blood gas analysis did not show metabolic acidosis during her first paralytic attack. This argues against the possibility of preexisting RTA, although we cannot rule out the possibility of unapparent incomplete RTA. The severity of RTA increased with repeated attacks. During the third attack 1 year after

the first attack, her blood pH was 7.3, but we did not evaluate for metabolic acidosis at that time. During her fourth attack, which occurred 3 months later, we detected the attack combined with metabolic acidosis (Table 2). The second reported case was a 34-year-old Chinese woman who had TPP and RTA and was positive for anti-Ro antibodies [2]. These findings were the same as those of our patient, but she did not have nephrogenic DI. As their patient's hyperthyroidism developed shortly before her admission, they suggested that preexisting RTA and subsequent thyrotoxicosis precipitated the hypokalemic periodic paralysis.

Nephrogenic DI appears to exacerbate the severity of hypokalemia caused by thyrotoxicosis and RTA. Nephrogenic DI is characterized by an inability of the kidney to concentrate urine because of insensitivity of the distal nephron to antidiuretic hormone. Acquired nephrogenic DI is secondary to the adverse effects of drugs, metabolic acidosis, hypokalemia, hypercalcemia and systemic diseases such as Sjögren's syndrome and hyperthyroidism [8, 9]. Our patient had hypokalemia, hyperthyroidism and distal RTA, which contributed to the development of nephrogenic DI.

Identification of the primary cause of hypokalemic periodic paralysis in our patient is difficult. It has been suggested that hyperthyroidism causes RTA by disturbing calcium metabolism and thus causes nephrocalcinosis [6, 10]. As our patient did not exhibit nephrocalcinosis, the possibility that hyperthyroidism contributed to the disturbance in calcium metabolism seems unlikely. The development of RTA after hyperthyroidism indicates that it is more likely that an autoimmune mechanism was responsible for the association between RTA and thyrotoxicosis. Our patient has anti-Ro antibodies but did not meet the criteria for Sjögren's syndrome. Because she has anti-Ro antibodies, Sjögren's syndrome may manifest itself at a later stage. As cases of Sjögren's syndrome with auto antibodies of thyroid and altered thyroid function have been reported, it is possible that an as yet unknown mechanism is responsible for the concurrent development of these diseases [7, 11–12].

We conclude that hypokalemic periodic paralysis caused by thyrotoxicosis and distal RTA, which contributed to the development of nephrogenic DI in our patient. Therefore, it is important to consider alternative precipitating causes when a patient exhibits features that are atypical of TPP. The paralytic attack did not recur after antithyroid treatment with maintaining euthyroid state. However, the distal RTA and nephrogenic DI still remained. The close observation and further treatment for RTA and nephrogenic DI are needed according to the patient's condition.

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