Recurrent Attacks of Hypokalemic Quadriparesis: An Unusual Presentation of Primary Sjögren Syndrome

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Abstract

We herein report the case of a 64-year old woman with recurrent attacks of hypokalemic quadriparesis which resulted from distal renal tubular acidosis (dRTA) secondary to Sjögren syndrome. The patient presented with sudden onset quadriparesis. A physical examination showed symmetric weakness of all four limbs. Severe hypokalemia (1.8 mEq/L), accompanied by normal anion gap metabolic acidosis, a positive urine anion gap and an inappropriately high urine pH pointed toward the diagnosis of dRTA. Further investigations disclosed primary Sjögren syndrome, which had not previously been recognized. On the basis of the current report and a review of the literature we suggest investigating the possibility of Sjögren syndrome in all patients with clinically unexplained dRTA.

Key words: paralysis, hypokalemia, Sjögren syndrome, renal tubular acidosis

(Intern Med 55: 1797-1800, 2016)

(DOI: 10.2169/internalmedicine.55.6453)

Introduction

Hypokalemic paralysis is a potentially life threatening emergency which requires rapid treatment along with a thorough evaluation to determine the underlying cause. The underlying etiologies of hypokalemia can be classified in two major categories: 1) acute conditions that cause the intracellular shifting of potassium without total body potassium depletion; and 2) total body potassium loss via excessive renal potassium excretion or extra-renal potassium loss due to vomiting or diarrhea.

Hypokalemic periodic paralysis (HPP) is a well-known cause of hypokalemic paralysis due to the trans-cellular shift of potassium, whereas distal renal tubular acidosis (dRTA) is an important cause of hypokalemic paralysis due to excessive renal potassium loss. As the clinical presentation of hypokalemic paralysis secondary to dRTA can be similar to HPP, the evaluation of the acid-base status and the urine anion gap is pivotal in the differentiation of these two diseases. The failure to differentiate dRTA from HPP may result in improper management, which can lead to the devel-

opment of potentially life threatening conditions.

We herein report the case of a 64-year-old Persian woman who experienced recurrent attacks of hypokalemic quadriparesis resulting from dRTA as the initial manifestation of Sjögren syndrome, which was previously misdiagnosed as HPP.

Case Report

A 64-year-old Persian woman was admitted to the emergency department of our hospital with quadriparesis. She reported the sudden onset of weakness of all four limbs and difficulty in getting out of bed on waking in the morning. She denied vomiting, diarrhea, diplopia, dysphagia, myalgia, or shortness of breath. She denied the use of diuretics, vigorous exercise or having eaten a carbohydrate-rich meal on the preceding day. She had no history of recent gastrointestinal or upper respiratory tract infection. Her family history was unremarkable. Her medical history revealed two episodes of hospital admission due to similar attacks of paralysis in the past month. In both episodes, severe hypokalemia had been documented and the patient's symptoms had com-

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Received for publication August 24, 2015; Accepted for publication September 13, 2015

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pletely resolved with administration of intravenous potassium chloride. She had been discharged with a diagnosis of HPP and no further evaluation for the etiology of hypokalemia had been carried out.

On physical examination, her vital signs were normal, with a blood pressure of 110/70 mmHg, a pulse rate of 68 beats/min and a body temperature of 36.8°C. Neurological examinations revealed symmetric weakness of both the proximal and distal muscles in the upper and lower limbs (muscle strengths ranging from 2-3/5). The patient's deep tendon reflexes were reduced in the four extremities. There were no fasciculations. Babinski's sign was bilaterally negative. A cranial nerve examination revealed no abnormalities. Other examinations were unremarkable. Her ECG showed normal sinus rhythm, a prolonged QT interval, but no U wave. The initial laboratory analysis revealed the following findings: blood glucose 115 mg/dL, sodium 138 mEq/L, potassium 1.8 mEq/L, calcium 9.1 mg/dL, phosphorous 2.5 mg/dL, magnesium 2.3 mg/dL, chloride 116 mEq/L, blood urea nitrogen 17 mg/dL, serum creatinine 1.1 mg/dL, albumin 4.1 g/dL and hemoglobin 12.5 g/dL. An arterial blood gas analysis showed pH 7.2, PCO₂ 32 mmHg, HCO₃ 12 mEq/L, indicating a hyperchloremic normal anion gap metabolic acidosis (serum anion gap: 10). Thyroid function tests revealed a TSH of 1.08 IU/mL (normal: 0.3-5.5 IU/mL), a T4 of 0.9 ng/dL (normal: 0.6-1.6 ng/dL) and a T3 of 88 ng/dL (normal: 75-200 ng/dL). A urine analysis showed a pH of 7.1, a specific gravity of 1.013 with 0-1 RBCs per high-power field (HPF), 4-6 white blood cells per HPF, and rare bacteria. Her urine culture was negative. A random urine sample revealed a potassium level of 42 mEq/L, a urine sodium level of 112 mEq/L and a urine chloride level of 138 mEq/L, indicating a positive urine anion gap. A diagnosis of dRTA was suspected according to the findings of hypokalemia, hyperchloremic normal anion gap metabolic acidosis, a positive urine anion gap and the patient's relatively high urine pH. The patient was initially treated with potassium chloride (10 mEq/h). Following the administration of potassium, the patient's potassium level gradually increased to 3.8 mEq/L over the ensuing day and her symptoms resolved completely.

The patient was admitted to the nephrology department to investigate the underlying cause. In order to confirm the diagnosis of dRTA, a sodium bicarbonate (NaHCO₃) loading test was performed with the administration of 1 mEq/kg/hour (60 mEq/hour) of intravenous NaHCO₃ solution. Urine and blood samples were taken at 1-hour intervals. When the patient's serum HCO₃ level increased to 22 mEq/L, her serum creatinine, urine creatinine and urine HCO₃ levels were 1 mg/dL, 21 mg/dL and 13 mEq/L, respectively. Accordingly, the fractional excretion of HCO₃ (FE-HCO₃) was determined to be 2.8%, which almost established the diagnosis of dRTA. Further investigations were performed to identify the underlying etiology of the dRTA. A further investigation of the patient's history revealed that she had been experiencing bouts of dry mouth for the previous 6 months; a symp-

tom which she had been trying to alleviate by drinking more water. She also noted itchy eyes and the sensation of a foreign body in her eyes for the previous 6 months. Subsequent immunological studies demonstrated positive antinuclear antibody (1:640) with a speckled pattern, anti-SSA (anti Ro) > 200 U/mL (normal <15 U/mL), anti-SSB (anti La) >200 (normal <15 U/mL), a relatively low C3 level of 82 mg/dL (normal 90-18 mg/dL) and a C4 level of 13 mg/dL (10-40 mg/dL). Results for anti-dsDNA and anti-Sm antibodies were negative. An ELISA test showed that the patient was negative for HBsAg, HBcAb, Anti HCV and Anti HIV. Serum protein electrophoresis revealed diffuse polyclonal hypergammaglobulinemia with slightly decreased albumin, along with elevated Beta-1 and gammaglobulin fractions [albumin fraction, 44.3% (normal 55.8-66.1%); Beta-1 fraction, 8.1% (normal 4.7-7.2%); gammaglobulin fraction, 37.7% (normal 11.1-18.8%); A/G ratio, 79%]. A urine test for Bence Jones protein was negative. Schirmer's test was positive in both eyes (right eye 3 mm/5 min; left eye 2.5 mm/5 min). The patient was diagnosed with primary Sjögren syndrome according to the revised version of American-European Consensus Group classification criteria (1). Treatment was initiated with potassium citrate (60 mEq/day, in two divided doses), hydroxychloroquine (400 mg daily) and prednisolone (30 mg/day) for one month followed by a slow taper. She was discharged with follow-up appointments with a rheumatologist and a nephrologist.

Discussion

We herein presented the case of a woman with recurrent attacks of quadriparesis due to severe hypokalemia that was previously misdiagnosed as HPP. However, at her most recent admission, she was diagnosed with dRTA, which eventually led to the diagnosis of previously unrecognized primary Sjögren syndrome.

Distal RTA is characterized by a defect in the excretion of H⁺ in the distal tubules, resulting in alkaline urine despite systemic acidosis; whereas proximal RTA (pRTA) is characterized by a decreased capacity for bicarbonate reabsorption in the proximal tubules, which leads to urinary bicarbonate wasting. There are several methods for distinguishing dRTA from pRTA. According to the biochemical features, the presentation of systemic hyperchloremic metabolic acidosis along with inappropriately alkaline urine (a urine pH of >5.6) points to the diagnosis of dRTA. These characteristic findings occur due to the diminished function of the H⁺-ATPase pumps in the distal tubules and collecting ducts, which makes the kidneys incapable of lowering urine pH in response to normal acid production (2). The NaHCO₃ loading test is another method that is commonly used in clinical practice for the differentiation of dRTA from pRTA. This test is performed by the administration of 1 mEq/kg/h NaHCO₃ to elevate the serum HCO₃ to 22-24 mEq/L and FE-HCO₃ is calculated at this serum bicarbonate level. This test is based on the concept that almost 90% of the filtered

HCO₃ is reabsorbed in the proximal tubule, while the remaining 10% is almost entirely reabsorbed in the distal tubules and collecting ducts. As a result, the FE-HCO₃ level is expected to be nearly zero in normal individuals; while in pRTA the FE-HCO₃ is >10%, while that in dRTA the FE-HCO₃ is 1-5% (3). Accordingly, in our case, the FE-HCO₃ level of 2.8% after the NaHCO₃ loading test almost established the presence of dRTA.

Distal RTA may occur as a primary and isolated entity, or be secondary to a number of hypergammaglobulinemic states, including systemic lupus erythematosus, Sjögren syndrome, primary biliary cirrhosis, chronic active hepatitis, autoimmune thyroid diseases, and chronic renal allograft rejection (2). In our patient, a history of sicca syndromes, positive Schirmer's test, and positive anti-SSA (anti Ro) and anti-SSB (anti La) antibodies were highly suggestive of the diagnosis of Sjögren syndrome. There are few studies in the literature in which hypokalemic paralysis resulting from dRTA is reported as the first manifestation of Sjögren syndrome (4-9). Distal RTA is found in nearly 30% of Sjögren syndrome patients; however, in the majority of them, dRTA is latent and asymptomatic (10). The exact pathophysiology for the development of dRTA in Sjögren syndrome is not fully understood. Some studies have addressed lymphocytic infiltrations surrounding the renal tubules, resembling the infiltrations that are seen in the exocrine glands, as the probable cause for renal tubular impairment (11). On the other hand, immunohistochemical studies have demonstrated the absence of H⁺-ATPase pump in the distal tubular cells in renal biopsies of patients with Sjögren syndrome and dRTA (12).

Kidney involvement in Sjögren syndrome can precede the onset of typical sicca symptoms. In a study on the renal biopsies of eight patients with kidney involvement secondary to Sjögren syndrome, two patients had renal lesions before the onset of clinical sicca symptoms (13). It is interesting that even attacks of hypokalemic paralysis resulting from dRTA in Sjögren syndrome can precede the onset of typical sicca symptoms. In one study, Cheng et al. reported two cases of hypokalemic quadriparesis as the first manifestation of Sjögren syndrome in which the patients did not have sicca symptoms or a positive Schirmer's test upon admission. Sjögren syndrome was diagnosed based on positive anti-SSA and anti-SSB results, after the exclusion of other autoimmune disorders. The index cases developed typical sicca syndrome and positive Schirmer's test at 5-month and 1-year follow-up examinations, respectively (8). In another study, Vaidya et al. reported a case that was similar to our own, wherein a 23-year old female was repeatedly admitted to hospital following weakness and fatigue due to hypokalemia. She had been misdiagnosed with congenital HPP in her previous admissions as she had promptly responded to potassium treatment. However, in the latest admission, the authors noticed the presence of dRTA and the patient revealed the recent onset of xerostomia and xerophthalmia. She was subsequently diagnosed with Sjögren syndrome (9).

It is interesting that the diagnosis of underlying Sjögren syndrome in the index case was only made when she developed typical sicca symptoms. These unusual clinical presentations of Sjögren syndrome may delay prompt diagnosis and effective treatment. On the basis of the current report and a review of the literature we suggest investigating the possibility of Sjögren syndrome in all patients with clinically unexplained dRTA, even in the absence of sicca symptoms.

The efficacy of corticosteroid therapy in Sjögren syndrome patients with dRTA who present with hypokalemic quadriparesis is controversial. Some authors suggest that steroid therapy should be considered in these patients as the presence of severe dRTA causing hypokalemic paralysis reflects the severity of the underlying autoimmune tubulointerstitial nephritis (3, 5-8). As an example, Soy et al. reported a primary Sjögren syndrome patient with dRTA who presented with symptoms of HPP. The index case had a normal renal function and renal biopsy was not performed. However, the authors administered steroid therapy as they hypothesized that hypokalemic quadriparesis due to dRTA was indicative of severe interstitial nephritis. They suggested that steroid therapy should be considered in patients with hypokalemic paralysis who do not respond to replacement treatment and in patients with recurring attacks (6). On the other hand, some authors have not administered steroid therapy for similar patients (4, 14). In the present case, our patient had frequent episodes of hypokalemic quadriparesis due to dRTA. We therefore administered steroid therapy to prevent any relapses of paralysis.

HPP and thyrotoxic periodic paralysis (TPP) are two important differential diagnoses in patients with hypokalemic paralysis. HPP is characterized by the sudden onset of flaccid paralysis that usually occurs on waking in the night or in the early morning. The most common form of HPP results from an autosomal dominant disorder of the voltage-gated sodium and calcium channels, which leads to abnormal intracellular potassium influx (15). TPP is a rare complication of hyperthyroidism that is predominantly seen in Asian males. Most cases do not manifest obvious signs or symptoms of hyperthyroidism at the onset of paralysis. In fact, it has been reported that only approximately 10% of patients show symptoms of hyperthyroidism at the presentation of TPP. As a result, it is mandatory to evaluate thyroid function tests in patients with hypokalemic paralysis, even in the absence of signs or symptoms of thyrotoxicosis (16).

Finally, certain drugs, especially diuretics, can induce severe iatrogenic hypokalemia, which may result in hypokalemic paralysis. In particular, acetazolamide can mimic the features of pRTA by inhibiting carbonic anhydrase in the renal proximal tubules, causing bicarbonate diuresis and metabolic acidosis (17-19). It is therefore essential to examine the history of drug intake in patients who present with hypokalemic paralysis.

Patients with acute flaccid paralysis in whom the initial biochemical studies show severe hypokalemia may be quickly overlooked and misdiagnosed with HPP. We suggest

the evaluation of the acid-base status, serum and urine anion gap as a simple and effective diagnostic approach for ruling out the presence of dRTA in these cases. In the presence of dRTA, further investigations should be carried out to identify the underlying cause, particularly with regard to the autoimmune diseases.

The authors state that they have no Conflict of Interest (COI).

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