Hypokalemic Paralysis: A Hidden Card of Several Autoimmune Diseases

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ABSTRACT: Acute hypokalemic paralysis is a rare and potentially fatal condition, with few related causes, one of which highlights distal renal tubular acidosis (dRTA). Distal renal tubular acidosis is a rare complication of several autoimmune diseases such as systemic lupus erythematosus, Sjögren's syndrome, and Hashimoto thyroiditis. We report a case of a lupic patient who presented rapidly progressive quadriparesis in the context of active renal disease. Research revealed severe refractory hypokalemia, metabolic acidosis, and alkaline urine suggestive of dRTA. We diagnosed Sjögren's syndrome based on sicca symptoms, an abnormal salivary glands' nuclear scan and the presence of anti-Ro/SSA and anti-La/SSB. In addition, the finding of thyroid peroxidase, thyroglobulin antibodies, and hypothyroidism led us to the diagnosis of Hashimoto thyroiditis. Due to the active renal involvement on the context of systemic lupus erythematosus and Sjögren's syndrome, the patient received immunosuppression with rituximab, resulting in a progressive and complete improvement.

KEYWORDS: lupus erythematosus, systemic, renal tubular acidosis, hypokalemias

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Introduction

Acute hypokalemic paralysis (AHP) is a potentially fatal but reversible condition which constitutes a challenge for emergency physicians. Secondary AHP is related to few conditions[1] and its ultimate course[2,3] can be avoided with a rapid correction of hypokalemia. A proper clinical evaluation aimed at determining its underlying cause should always take place. One of its main causes, but many times overseen, is distal renal tubular acidosis (dRTA), which is a disorder characterized by an abnormal tubular acidification, resulting in hypokalemia and hyperchloremic metabolic acidosis with a normal serum anion gap (AG). Not frequently, dRTA could lead to AHP. Autoimmune disorders such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), and Hashimoto thyroiditis (HT) may cause secondary dRTA[4,5] and should always be excluded. We report the case of a patient with AHP secondary to dRTA, with more than one autoimmune disorder commonly associated with this condition, who had a good response to immunosuppression with rituximab (RTX).

Case Presentation

A 45-year-old woman was admitted to the emergency service with a 3-hour condition of tachypnea and flaccid quadriparesis. She had a 7-year history of SLE (her initial symptoms were malar rash, photosensitivity, nonerosive polyarthritis, and positive antinuclear antibodies with homogeneous pattern, titer 1/2560) whose main involvement was a proliferative glomerulonephritis and a recent diagnosis of hypothyroidism. Systemic lupus erythematosus was treated with prednisone (PDN) at varying doses and hydroxychloroquine and mycophenolate mofetil (MMF) with doses between 1.5 and 3 g/d (current dosage) with complete renal response. Before 10 months of this episode, she presented a proteinuric flare (24-hour urine protein test: 760 mg/dL) poorly followed due to the lack of patient's compliance. Before 3 weeks of admission, she began complaining of mild myalgias and cramps which she attributed to her job. On admission, the patient denied vomiting, diarrhea, and the use of other drugs besides her usual medications. Her biologic functions were normal. She was tachypneic, tachycardic, with a normal blood pressure. Arterial blood gases demonstrated metabolic acidosis with normal serum AG, hypoxemia, and severe hypokalemia (K: 1.4 mEq/L) with electrocardiogram changes (presence of U wave and flattening of the T wave). Laboratory tests showed serum potassium at 1.7 mEq/L, high titers of anti–double-stranded DNA, and low complement. Cortisol, glucose, creatinine, calcium, magnesium, and liver profile were normal, and creatine kinase was mildly elevated (246 U/L). Urinalyses showed telescoped urinary sediment—an alkaline urinary pH (7.8). A renal ultrasonography revealed bilateral chronic nephropathy.

She received 2 intravenous replacement doses of potassium (5.4 mEq), but serum potassium remained low (1.7 mEq/L). She was admitted to the Rheumatology Department tachypneic with flaccid quadriparesis. Despite intense potassium replacement therapy, serum potassium remained in the hypokalemic range (<2.5 mEq/L) with persistent respiratory distress. Therefore, other possible causes of respiratory distress

such as pulmonary thromboembolism (normal lung scintigraphy), pulmonary hypertension, and pericardial effusion (determined by echocardiography) were ruled out. Clinical improvement was evident (normal respiratory rate and pattern and the ability to stand, walk, and sit up in bed unassisted) a few hours after a continuous potassium infusion pump was placed. Potassium replacement was continued with an oral solution of citric acid (Shohl's modified solution). In addition, the diagnosis of HT was confirmed on the context of high antithyroid peroxidase and antithyroglobulin antibody titers, and SS was diagnosed based on a 6-month history of sicca symptoms, a compatible salivary glands' nuclear scan, a positive rose bengal staining test, and positive anti-Ro/SSA and anti-La/SSB antibodies. Neither a kidney nor a salivary gland biopsy could be obtained due to patient's refusal. Finally, we confirmed the diagnosis of dRTA with alkaline urine (pH of 7.5) and positive urinary AG of +63 mEq/L (urine Na^+ of 265 mEq/L, K^+ of 38 mEq/L, and Cl^- of 240 mEq/L).

Active SLE with renal involvement despite optimal treatment with MMF was confirmed (SLEDAI [Systemic Lupus Erythematosus Disease Activity Index] 2K was 18), so we increased the PDN dose (0.5 mg/kg/d) and started RTX 1 g biweekly. Patient was discharged with a strength of 4+/5 in proximal muscles of scapular grip, 5/5 in proximal muscles of pelvic grip, and with normal serum potassium levels (3.9 mEq/L). The patient has been followed up periodically; her muscle strength has remained normal, as well as her serum potassium levels. In addition, she has remained in clinical remission until the present (2 years after the event).

Discussion

The sudden onset of flaccid quadriparesis is an unusual but potentially lethal clinical condition seen in emergency departments. In our patient, the origin of her symptoms was severe hypokalemia, which led to paralysis and weakness of the respiratory muscles, which in turn contributed to hypoxemia. Acute hypokalemic paralysis is a relatively rare, potentially reversible cause of acute weakness; mortality occurs secondary to cardiac arrhythmias and respiratory failure.[1,2] Therefore, it is of the utmost importance to consider it within the differential diagnosis in patients with this clinical condition. Hypokalemic paralysis can be primary or secondary, both lead to similar symptomatology. However, one of their main differences is the presence of an acid-base disorder in most of the patients with a secondary cause, plus the age of presentation in the primary form usually is under 25 years old and is predominant in men. Because the primary causes are finally determined by discarding, a meticulous analysis of all possible secondary causes is necessary. Fortunately, the causes of secondary AHP are limited (Table 1).[3] Our patient was normotensive and denied vomiting, diarrhea, and the use of drugs other than her usual medications. Thyrotoxic paralysis, condition usually associated with iatrogenic thyrotoxicosis,[4] was also excluded because our patient had not modified her levothyroxine doses, and her thyroid-stimulating hormone (TSH) and triiodothyronine (T3) were normal (TSH: 0.82 mUI/L; T3: 4.0 pg/mL).

Table 1. Common causes of hypokalemic paralysis.

a. Periodic paralysis due to intracellular shift
Thyrotoxic periodic paralysis
Hypernatremic hypokalemia paralysis
b. Patients with hypokalemic paralysis due to potassium deficit
With hypochloremic metabolic alkalosis Excessive vomiting Diuretics Bartter or Gitelman syndrome Primary aldosteronism
With hyperchloremic metabolic acidosis Distal renal tubular acidosis Acute severe diarrhea

Modified with permission from Lin et al.[3]

The diagnosis of dRTA was established on the basis of hyperchloremic metabolic acidosis with normal AG, alkaline urine, positive urinary AG (urine Na^+ of 265 mEq/L, K^+ of 38 mEq/L, and Cl^- of 240 mEq/L) and severe, refractory hypokalemia. In this disorder, the abnormal metabolic profile is a result of an excessive renal loss of potassium due to impaired secretion of H^+ in the distal nephrons.[5] It has distinctive features and could have a primary or secondary cause (Table 2).[5–7] Acquired dRTA is often secondary to autoimmune diseases[5,8] (SLE, SS, and HT, among them).

In HT, only a few cases of RTA have been reported. In murine models, thyroid hormones have been related to an abnormal expression of acid-base transporters, with increased membrane cell Na^+/K^+-ATPase pumps and reduced elimination of H^+ ions in the distal nephron.[10] The existence of antibodies against the collector tubules has been suggested as possible cause[8] supporting the occasional need for corticosteroid treatment in these patients.[11] The prevalence of dRTA in SLE has not been asserted properly because of the few reported cases. Of note, concurrent active proliferative glomerulonephritis and RTA have been described.[12,13] The precise mechanisms of tubular damage in SLE have not been elucidated yet; however, the deposition of immunoglobulins, complement, and plasma cells around tubules which may lead to irreversible damage suggests that the ongoing SLE autoimmune process is involved in its pathogenesis.[14]

In contrast to HT and SLE, tubulointerstitial renal involvement is a relative common manifestation of SS with an estimated prevalence of 5% to 10%.[15–20] The pathogenesis of dRTA in SS is not completely understood, but some studies suggest that the absence of H^+-ATPase pump and the presence of autoantibodies to intercalated cells in the collector duct and against carbonic anhydrase in the distal nephron are the

Table 2. Conditions associated with distal RTA.

PRIMARY	SECONDARY
Autosomal-dominant RTA	Sjögren's syndrome
Autosomal-recessive RTA	Systemic lupus erythematosus
Pseudohypoaldosteronism type II	Chronic active hepatitis
	Hashimoto thyroiditis
	Takayasu arteritis
	Myeloma

Abbreviation: RTA, renal tubular acidosis.
Modified with permission from Laing et al.[7]

pathogenic mechanisms.[21,22] Besides, there is a prominent interstitial infiltrate of lymphocytes and plasma cells,[18,19,23] which invade the tubular membrane and lining epithelium, change the architecture, and generate a secretory defect in the distal tubules. Other facts that might support an autoimmune etiology in SS is a higher proportion of antinuclear, anti-Ro/SSA, and anti-La/SSB antibodies[20,24] plus the correction of the urinary acidification after treatment with cyclophosphamide.[25] Distal renal tubular acidosis is generated due to tubulitis and/or tubular atrophy,[26] leading to the complete loss of H+-ATPase pumps in the collecting ducts. Their presence is valued as a more severe compromise[27] and is valued within the ESSDAI (EULAR Sjögren's syndrome disease activity index) score as low or moderate according to the presence of renal failure.[28] Early treatment with immunosuppressive drugs has been shown to maintain or improve renal function.[26]

Although severe hypokalemia due to dRTA is rarely seen in autoimmune diseases,[29–33] this condition can be life-threatening and could reflect the severity of the underlying autoimmune tubulointerstitial nephritis implicating the need for immunosuppressive treatment. Our patient presented tubular compromise associated with a refractory glomerular involvement and had a good response to RTX treatment. Of the tubulointerstitial nephritis cases reported in patients with SLE,[34–37] to our knowledge, a favorable response to RTX has been reported in only one case.[38] In Sjögren's tubulointerstitial nephritis, there are few previous case reports in which RTX has been used.[26] Given the presence of tubulointerstitial involvement, the use of RTX can be supported on the basis of ectopic germinal centers and B-cell and T-cell aggregates, which have been strongly associated with the deposition of immune complexes in the renal tubules' basement membrane which are found in these patients.[39–45]

In our patient, both SLE and SS could explain the tubulointerstitial compromise; however, in the presence of active glomerular involvement and because the severity of interstitial inflammation could predict progression to renal insufficiency,[46] our medical decision was to initiate RTX.

In conclusion, hypokalemia could be an inadverted cause of flaccid paralysis and might even lead to death. Besides, refractory hypokalemia associated with metabolic acidosis should suggest the diagnosis of dRTA and lead to the search of secondary causes, being the autoimmune diseases (SLE, SS, and less frequently HT) the most important among them. Finally, potassium replacement and immunosuppressive treatment should be individually adjusted to each patient; long-term follow-up should monitor muscle strength, serum electrolytes, and renal function.

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Author Contributions

All authors were responsible of case conception, critical revision and drafting of the manuscript. All authors approved the final version to be published.

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