Case Report

Hypokalemic Paralysis due to Primary Sjögren Syndrome: Case Report and Review of the Literature

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Tubulointerstitial nephritis (TIN) is the main renal involvement associated with primary Sjögren syndrome (pSS). TIN can manifest as distal renal tubular acidosis (RTA), nephrogenic diabetes insipidus, proximal tubular dysfunction, and others [1], of which RTA is the main clinical presentation [2]. RTA has been reported in 4.3 to 9% of pSS patients; it is more common in middle-aged women, and two-thirds of them will develop symptoms [2, 3]. Hypokalemic paralysis is the initial symptom in seven percent of patients with Sjögren's syndrome [4]. We present a case of paralysis due to RTA in a pSS patient and also discuss the treatment in these patients.

1. Introduction

Sjögren's syndrome is an autoimmune disease with glandular (salivary and lacrimal) and extraglandular (neurologic, renal, hepatic, respiratory, cardiovascular, and cutaneous) manifestations. Tubulointerstitial nephritis (TIN) is the main renal involvement associated with primary Sjögren syndrome (pSS). TIN can manifest as distal renal tubular acidosis (RTA), nephrogenic diabetes insipidus, proximal tubular dysfunction, and others [1], of which RTA is the main clinical presentation [2]. RTA has been reported in 4.3 to 9% of pSS patients; it is more common in middle-aged women, and two-thirds of them will develop symptoms [2, 3]. Hypokalemic paralysis is the initial symptom in seven percent of patients with Sjögren's syndrome [4]. We present a case of paralysis due to RTA in a pSS patient and also discuss the treatment in these patients.

2. Case Report

A 31-year-old female presented to the emergency room due to a 3-day history of progressive weakness and pain of the upper and lower extremities until walking was impossible. Two days before admission, cramps and generalized dysesthesias were evidenced. On admission, the patient presented mild dyspnea. Her past medical record was significant for polyarthralgias in carpal, metacarpophalangeal, and proximal interphalangeal joints and dry mouth for the past three months. She denied use of alcohol, illicit drugs, or herbal medicines. Her vital signs on admission were a temperature of 36.3°C, a heart rate of 54 beats per minute, a respiratory rate of 20 breaths per minute, oxygen saturation of 97% at room air, capillary blood glucose of 103 g/dL, and blood pressure of 100/60 mmHg. On physical examination, the deep tendon reflexes were globally diminished, her muscle strength, both proximal and distal, was 3/5 on Lovett's scale, and her tongue was dry and the infralingual salivary pooling was absent. Remarkable laboratory tests are shown in Table 1.

A panoramic photo of minor salivary gland biopsy is shown in Figure 1. With all lab results, a distal RTA (dRTA) diagnosis due to pSS was made. Hypokalemia and metabolic acidosis were treated with intravenous potassium chloride and
Table 1: Laboratory investigation.

| Laboratory investigation | Result |
|--------------------------|--------|
| CBC                      | Hemoglobin: 14.7 g/dL, WBC: 8.7 × 10³, lymphocytes: 0.683 × 10³, platelets: 159 K/µL |
| Serum electrolytes       | Sodium: 138.2 mmol/L, potassium: 2.7 mmol/L, chloride: 101 mmol/L |
| Serum chemistry          | Glucose: 123 mg/dL, creatinine: 0.8 mg/dL, urea nitrogen: 13 mg/dL |
| Liver panel              | AST: 19 IU/L, ALT: 13 IU/L, albumin: 4.2 g/dL, total bilirubin: 0.7 mg/dL |
| Urinalysis               | pH: 8, leucocytes: 0–2/HPF, erythrocytes: 0/HPF, tubular cells: 0/HPF |
| Urinary electrolytes     | Sodium: 114 mmol/L, potassium: 32 mmol/L, chloride: 57.3 mmol/L, creatinine: 31.8 mg/dL |
| Urinary anion gap        | 76 mmol/L |
| Blood gas                | pH: 7.12, HCO₃⁻: 21 mmol/L, pO₂: 31 mmHg, pCO₂: 37 mmHg, saturation: 37% |
| Serum anion gap          | 10 mEq/L |
| Thyroid panel            | TSH: 2.06 µIU/mL, free T4: 0.94 ng/dL |
| Acute phase reactants    | ESR: 31 mm/h, CRP < 0.5 mg/L |
| Virus panel              | HIV-negative, HBV-negative, HCV-negative |
| Rheumatoid factor        | IgM: 155.7 IU/mL, IgG: 6.7 IU/mL, IgA: 12.2 IU/mL |
| ANAs by IFA              | 1: 5120 fine speckled |
| SSA/SSB by ELISA         | 200.14/19.67 IU/mL |
| Unstimulated whole saliva flow, without anesthesia | 1.4 mL/15 minutes |
| Minor salivary gland biopsy* | Positive, focus score of 5 |
| Schirmer's test          | Right eye: 7 mm, left eye: 10 mm |

*According to [5].

Figure 1: A panoramic photo of minor salivary gland biopsy. A chronic lymphocyte focal sialadenitis was observed.

sodium bicarbonate. Then, we initiated hydroxychloroquine. The patient was discharged and we followed her up in our clinic every two months for the next eight months. She was reported to be asymptomatic with the use of potassium citrate only.

3. Discussion

A recent set of classification criteria for pSS were published by the ACR/EULAR in 2016 [6] and this applies to the individual that has a score of ≥4. According to this, the diagnosis of this autoimmune disease was made in our patient (labial salivary gland with a focus score of ≥1, anti-SSA positive, and an unstimulated whole saliva flow of less than 0.1 mL/min). Renal involvement in pSS is the result of two distinct pathophysiological processes: TIN and glomerulopathy [1]. The tubulointerstitial inflammation is the most common renal lesion described by Talal et al. [7]. dRTA prevalence fluctuates between 5 and 70%, according to population studies [4, 8, 9]. dRTA can be classified as complete or incomplete; the former is characterized by metabolic acidosis with morning urine pH > 5.5 and a positive urinary anion gap. The incomplete form presents with normal serum bicarbonate levels but urinary pH fails to fall to <5.3 after ammonium chloride loading [10]. The pathogenetic mechanism of this complication is not completely understood. Antibodies to vacuolar H+-ATPase and anion exchanger 1, as well as antibodies to carbonic anhydrase II, have been implicated in the pathogenesis [11–13]. Another hypothesis is a defective S-phase-kinase-associated protein-1, a component of the regulator of the ATPase of vacuolar and endosomal membranes that could induce a defective V-ATPase assembly [14]. Also, a possible relation between antibodies anti-SSA/Ro and dRTA has been described as one pathogenic mechanism of development [15].

Hypokalemia is the most common electrolyte abnormality in patients with dRTA. The causes of hypokalemia include decreased distal tubular Na delivery, secondary hyperaldosteronism, defective H-KATPase, and bicarbonaturia [16]. Hypokalemic paralysis may precede sicca syndrome from three months to four years in patients with a final diagnosis of pSS [17, 18].

Renal biopsy is not mandatory in these patients [2], but it may help us evidence the inflammatory mechanisms that trigger the disease. As has been demonstrated by Evans et al. in twelve patients with TIN secondary to pSS, they observed CD4+ T-cell predominance in biopsies, similar to those seen
| Reference                | Type of study | Number of patients | Age (years) | Extraglandular manifestations besides dRTA | Treatment                                      | Follow-up | Outcome                        |
|--------------------------|--------------|--------------------|-------------|---------------------------------------------|------------------------------------------------|-----------|--------------------------------|
| Goroshiet al.            | Case series  | 13                 | 33.1        | Arthritis, arthralgias, vasculitis           | Extraglandal, HCQ, and MTX                      | Symptomatic | No improvement in reduction of HCO₃ or K requirements |
| Khabgawat et al.         | Report of cases | 2                  | 20.5        | Arthritis, myalgia, nephrolithiasis         | Symptomatic, and methyprednisolone              | No         | Stable clinical evolution      |
| Soy et al.               | Case report  | 39                 | 76          | Nephrocalcinosis                            | Symptomatic, and montelukast                   | Symptomatic | Relapse after stopping treatment |
| Kawashima et al.         | Case report  | 1                  | 39          | Osteomalacia, interstitial nephritis         | Symptomatic, and prednisolone                  | No         | Stable clinical evolution      |
| Corner et al.            | Case report  | 1                  | 43          | No                                          | Symptomatic, and prednisolone                  | 2 years    | Stable clinical evolution      |
| Servin et al.            | Case report  | 1                  | 64          | No                                          | Symptomatic, and HCQ                           | Not reported| 1.5 years                     |
| Vaidya and Ganeshpure et al. | Report of cases | 2              | 23          | No                                          | Symptomatic                                   | Not reported| Stable clinical evolution      |
| Rao et al.               | Report of cases | 3               | 35          | No                                          | Symptomatic                                   | Not reported| Stable clinical evolution      |
| Naile et al.             | Case report  | 1                  | 65          | No                                          | Symptomatic                                   | Not reported| Stable clinical evolution      |
| Rajagopala et al.        | Case report  | 1                  | 36          | Medullary nephrocalcinosis, recurrent CNS demyelination, nevrotic spinal demyelination, Secondary APS with thrombosis | Symptomatic, and methyprednisolone, CYC, and AZA | Not reported| Stable clinical evolution      |
| Daar et al.              | Case report  | 1                  | 58          | Low-grade fever                              | Symptomatic                                    | Not reported| Stable clinical evolution      |
| Singh et al.             | Case report  | 1                  | 40          | No                                          | Symptomatic                                    | Not reported| Stable clinical evolution      |
| Chang et al.             | Report of cases | 2               | 30          | One patient: carotid artery stenosis        | No                                             | Not reported| Stable clinical evolution      |
| Eriksson et al.          | Case report  | 6                  | 10          | No                                          | Not reported                                   | Not reported| Stable clinical evolution      |
| Taylor and Parsons       | Case report  | 1                  | 55          | No                                          | Symptomatic                                   | Not reported| Stable clinical evolution      |
| Carniati et al.          | Case report  | 1                  | 32          | No                                          | Symptomatic                                   | Not reported| Stable clinical evolution      |
| Reference         | Type of study | Number of patients | Age (years) mean | Extraglandular manifestations besides dRTA | Treatment | Follow-up | Outcome                   |
|-------------------|---------------|--------------------|------------------|-------------------------------------------|-----------|-----------|---------------------------|
| Muthukrishnan et al. | Case report   | 1                  | 39               | No                                        | Symptomatic and prednisolone | 2 years   | Stable clinical evolution |
| Prakash et al.     | Case report   | 1                  | 49               | No                                        | Symptomatic, methylprednisolone, prednisolone | 16 days   | Died                      |
| Skalova et al.     | Case report   | 1                  | 16               | No                                        | Symptomatic, methylprednisolone, CYL | Not reported | Stable clinical evolution |
| Liao et al.        | Case report   | 1                  | 49               | Not reported                              | Symptomatic | Not reported | —                         |
| Sengul et al.      | Case report   | 1                  | 48               | No                                        | Symptomatic, prednisolone, HCQ | Not reported | —                         |
| Yilmaz et al.      | Case report   | 1                  | 53               | No                                        | Symptomatic, methylprednisolone, HCQ, AZA | 10 days   | Stable clinical evolution |
| Logan and Ahmed    | Case report   | 1                  | 36               | No                                        | Symptomatic, HCQ | 3 years   | Stable clinical evolution |
| Fujimoto et al.    | Case report   | 1                  | 27               | Kidney lithiasis                          | Symptomatic | 4 months   | Stable clinical evolution |
| Mugundhan et al.   | Case report   | 1                  | 38               | Nephrocalcinosis                          | Symptomatic and prednisolone | Not reported | —                         |
| Garza-Alpirez et al. | Case report  | 1                  | 31               | Polyarthritis                             | Symptomatic, HCQ | 8 months   | Stable clinical evolution |

Symptomatic: potassium (K) and bicarbonate (HCO₃⁻); HCQ: hydroxychloroquine; MTX: methotrexate; CYC: cyclophosphamide; AZA: azathioprine; MM: mycophenolate mofetil; CYL: cyclosporine A; APS: antiphospholipid syndrome; extraglandular manifestation: arthritis, arthralgia, and vasculitis.
in lip salivary glands [19]. Also, similar lymphocytic infiltrates around renal tubules have been observed [20]. More data from prospective studies of pSS biopsies are needed in order to enhance knowledge in these subsets of patients and also to determine the best treatment.

dRTA treatment includes potassium restitution before alkali therapy, because the last might aggravate hypokalemia by enhancing the shift of potassium into cells and bicarbonaturia [21]. In the beginning, hydroxychloroquine was started in the suspicion of a secondary cause of Sjőgren’s syndrome but it was later discontinued.

RTA is not a usual indication for immunomodulatory therapy in pSS, even though it is an extraglandular manifestation [22]. Steroid therapy in cases that are nonresponsive to replacement therapy and in those with recurring hypokalemic paralysis attacks is indicated [23].

We searched in MEDLINE, IMBIOMED, and Google Scholar for clinical cases of hypokalemic paralysis due to pSS. We included only articles written in English or Spanish. In Table 2, we describe each one of them: number of cases, age of patients, extraglandular manifestations besides dRTA, treatment, and outcome. We found fifty-two cases for analysis but we included only cases with a complete report of treatment [15, 21–47]. We observed the highest frequency of this clinical presentation in young adults of the female gender. It is important to note that, in some cases, dRTA was present before the diagnosis of pSS. All patients received symptomatic treatment. We noted that 25% (13/52) received corticosteroids. Of these patients, 61% (8/13) did not report extraglandular manifestations, besides dRTA. The outcomes (at different duration) were clinically stable in 61% (8/13), 8% (1/13) had a relapse after treatment was stopped, 8% (1/13) died from an infectious cause, and 23% (3/13) did not report the outcome.

On the other hand, 32.6% (17/52) received only symptomatic treatment. Of these patients, 41% (7/17) did not report extraglandular manifestations. Only in six (35%) patients was the outcome reported, of whom 83% (5/6) were clinically stable, and in 17% (1/6) four relapses occurred.

In the early diagnosis era of autoimmune diseases (like in rheumatoid arthritis), the importance of recognizing kidney involvement before glandular symptoms appear has been observed previously [21, 25, 28]. Also, we consider it important to determine whether some factors can trigger the beginning of this manifestation. This association has been observed by Logan and Ahmed. They described in a patient the use of Echinacea as a trigger of pSS [45]. Perhaps this means that the immunological tolerance is already lost, and some infections or substances can precipitate the clinical disease. We agree with the recommendation given by François and Mariette to screen all pSS patients according to manifestations every six to twelve months [10].

With such heterogeneous information, prospective studies are needed to assess the value of adding corticosteroids as a standardized treatment of this manifestation. We may consider that, in cases of hypokalemic paralysis in which there is a potentially life-threatening presentation, the treatment with corticosteroids could be justified.

**Conflicts of Interest**

The authors declare that there are no conflicts of interest regarding the publication of this article.

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