

Hypokaliemia in primary Sjogren's Syndrome

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Abstract

Sjögren syndrome (SS) is classified as an autoimmune disorder where the immune system primarily attacks the lacrimal and salivary glands impairing the glands ability to secrete fluids. Immune system may also attack other organs and tissues. Sjogren syndrome is classified as primary or secondary, depending on coexistence of other autoimmune disease. It affects predominantly middle-aged women, with a female to male ratio reaching 9:1 [1]. We present a 35 year old female patient with suspected diagnose of Sjögren's syndrome and flacid quadriplegia caused by hypokaliemia in RTA type 1.

Keywords: Sjogren's syndrome; Quadriplegia; Hypokaliemia; Distal renal tubular acidosis type 1

Abbreviations: SS: Sjögren Syndrome; RTA: Renal Tubular Acidosis; NHL: Non-Hodgkin Lymphoma; MALT: Mucosa-Associated Lymphoid Tissue; NMZL: Nodal Marginal Zone Lymphomas; DLBCLs: Diffuse Large B-cell Lymphomas; AECG: American-European Consensus Group; ACR: American College of Rheumatology; CCM: Clinical Center of Montenegro; ER: Emergency Room; UL: Upper Limb; LL: Lower Limb; T Reflex: Tendon Reflex; ANA: Antinuclear Antibodies; HGB: Hemoglobin; MCV: Mean Corpuscular Volume; ABB: Acid Base Balans; pH: Potential Hydrogen; pCO₂: Partial Pressure of Carbon Dioxide; pO₂: Partial Pressure of Oxygen; STD: Standard Bicarbonate; PTH: Parathyroid Hormone; EMNG: Electromyoneurography; EGDS: Esophagogastroduodenoscopy; CT Scan: Computerized Tomography Scan; MRI: Magnetic Resonance Imaging; pSS: Primary Sjogren's syndrome

Introduction

Sjögren syndrome is a systemic chronic inflammatory disorder characterized by lymphocytic infiltrates in exocrine organs. The symptoms most associated with this autoimmune disorder involves sicca symptoms such as xerophthalmia (dry eyes) and xerostomia (dry mouth). Other organ systems may be affected in many patients. We can find Raynaud's phenomenon, cutaneous vasculitis, pulmonary disease, lymphadenopathy, renal involvement, peripheral neuropathy, gastrointestinal symptoms such as dyspepsia, diarrhoea, constipation [2]. They are at increased risk for coeliac sprue. Sjögren syndrome (SS) has been associated with the development of non-Hodgkin lymphoma (NHL). Mucosa-associated lymphoid tissue (MALT) lymphomas constituted the majority (59%) of NHL subtypes, followed by nodal marginal zone lymphomas (NMZLs) (15%) and diffuse large B-cell lymphomas (DLBCLs) (15%) [3]. Primary Sjögren's syndrome has been called an autoimmune epithelitis, since the lymphocytic infiltrate is centred on epithelial cells in each organ that it affects. Renal

involvement in pSS is the result of two distinct pathophysiological processes: epithelial disease with a predominantly mononuclear lymphocytic infiltration resulting in tubulointerstitial nephritis and non-epithelial disease with a secondary immune complex-mediated process resulting in glomerulopathy [4]. Tubulointerstitial nephritis remains the most common presentation of renal involvement and can cause different defects in tubular function. This is often characterised by a distal RTA type 1 and less commonly proximal RTA type 2. Cortical collecting duct dysfunction leads to distal renal tubular acidosis (RTA type 1). Glomerulus involvement is less often. Requirement for histopathological studies it is not essential for diagnosis of RTA, but it is highly recommended for confirmation glomerulonephritis. The results of renal biopsy disclosed membranoproliferative, proliferative and membranous glomerulonephritis and cryoglobulinemic-mediated glomerular damage [5].

There are two different classification criteria for diagnose, what is represented at the Table 1 below. In 2002 American and European experts allowed the formulation of the American-European Consensus Group (AECG) criteria, and in 2012 a group of American experts endorsed by American College of Rheumatology (ACR) proposed another set of classification criteria, ACR criteria. We did not mentioned all set of AECG criteria, but only the tests we use in clinical practice (pragmatic AECG criteria); that is, only the unstipulated whole salivary flow to assess salivary gland involvement (and not salivary scintigraphy or parotid sialography which are considered obsolete by most physicians), and only the Schirmer's test to assess ocular signs (and not vital dye staining graded according to van Bijsterveld method).

Exclusion criteria for both criteria sets are head-and-neck radiation, graft-versus-host disease, hepatitis C infection, acquired immunodeficiency syndrome or sarcoidosis. Pre-existing lymphoma and use of anticholinergic drugs are exclusion criteria only in the AECG criteria, whereas amyloidosis and IgG4-related disease are exclusion criteria only in the ACR criteria [6].

	Pragmatic 2002 AECG criteria	2012 ACR criteria
Items	1. Ocular dryness symptoms	1. Positive anti-SSA or anti-SSB antibodies or positive rheumatoid factor plus ANA \geq 1:320
	2. Oral dryness symptoms	2. Focus score \geq 1 focus/4 mm ² on minor salivary gland biopsy
	3. Ocular signs: Schirmer's test \leq 5 mm/5 mins	3. Kerato-conjunctivitis sicca with ocular staining score \geq 3
	4. Focus score \geq 1 focus/4 mm ² on minor salivary gland biopsy	
	5. Salivary gland involvement: unstimulated whole salivary flow \leq 0.1 ml/min	
	6. Positive anti-SSA or anti-SSB antibodies	
Rules for classification	Presence of any four of the six items with at least item 4 or 6, or presence of any three of the four objective items (items 3, 4, 5 and 6)	In a patient with suspected Sjögren's syndrome, any two of the three items

Table 1: Pragmatic AECG [1] and ACR [2] classification criteria for Sjögren's syndrome.

Case Report

A 35 years old female patient was admitted to the Clinical Center of Montenegro (CCM) via emergency room (ER) at the Department of Rheumatology due to her conspicuous weakness, moving inability, lower and upper extremities numbness and neck stiffness. Those difficulties started three days before the admission with sub-febrile temperatures, around 37°C, with a slight fatigue. She noticed some small rash across her body and the localized erythematous change on her forearm. As the muscular weakness was more prominent, the patient went to the General Hospital. She was screened by neurologist on the admission, who noted a conspicuous weakness of the neck flexors and also a weakness in proximal and distal muscular groups UL (upper limbs) and LL (low limbs). MT (musculo-tetive) reflexes were symmetric on both sides. Swallowing difficulty was also detected. The performed laboratory analyzes indicated the presence of noticeable hypokalemia (K 2.06...1.35). The therapy included pulse dose of corticosteroids, potassium preparations and proton pump inhibitors. Considering that there was no significant improvement of the patient's condition, she was referred to the CCM for the further treatment. In anamnesis, patient mentioned suspected SS, she was taking occasionally corticosteroids and also an antimalarial therapy over the past six months. The final diagnosis of SS was not established because of insufficient diagnostic criteria. Due to the numbness, eyes and mouth dryness, and difficult swallowing, the biopsy of salivary glands was done, the pathohistological findings indicated a deficient of the lymphocyte infiltration without exact information about focus score. Schirmer's test was negative. Immunological analyses were in favor of SS: ANA speckled type 4+, anti Ro (SS/A) 185, anti La (SS/B)>200, anti CCP 69.9. Positive family history of SS and Sarcoidosis.

During the admitting to the ER the patient was aware, well orientated, eupnoic in inactive state, afebrile, anicteric, acyanotic, with dry coated tongue and inability to stand alone. She was giving the impression of a moderately severe patient. The skin was with a diminished turgor with no signs of hemorrhagic syndrome. Lymph nodes were inconspicuous. Cardio-respiratory also stable. Neurological examination showed a flaccid quadriparesis. First laboratory tests at ER showed hypokalemia (K 1.5), increased number of leukocytes (Le 18.7) and microcytic anaemia (Hgb 104, MCV 93.5). Hospital treatment was indicated. At the Rheumatology department the level of

electrolytes and abb were daily controlled. In lab-analysis we confirmed hypokalemia, leucocytosis and anaemia. Laboratory examination results are presented in Table 2. ABB (acido-base bilans) showed the presence of metabolic acidosis with a regular anion-gap (Table 3).

Parameters	Values		Units	Reference range
Erythrocytes	3.07	3.28	10 ¹² /l	4.50-5.80
Hemoglobin	99	108	g/l	130-170
Platelets	166	192	10 ⁹ /l	150-400
Leukocytes	19.62	11	10 ⁹ /l	4.00-10
Glucosa	7.3	4	mmol/l	4.6-6.4
Urea	5.6		mmol/l	3.0-9.2
Creatinine	73		ηmol/l	62-106
Albumins	38	42	g/l	35-52
Alanine aminotransferase	13	41	IU/l	<33
Calcium	2.22	2.13	mmol/l	2.10-2.55
Kalium	3	3.4	mmol/l	3.5-5.1
Sodium	144	143	mmol/l	136-145
Chloride	107.3	107.3	mmol/l	97-108

Table 1: Laboratory values during hospitalization.

The performed biochemical analysis of 24 h urine with 4200 ml, was found to be normal. New immunological analyses were performed and they corresponded to the previous ones. Anti Ro (SS/A) At 149 and anti La (SS/B) At 163. The increase of antibodies characteristic for coeliac disease was noted (anti TTG IgG 5, anti TTG IgA 47). Cryoglobulins were also positive. Other biochemical analyses were in normal range. Blood hormone analysis, except the reduced level of parathyroid hormone (PTH) was normal. Tumor markers, with the exception of beta-2-microglobulin and chromogranin, were normal,

too. Lung radiography was normal with calciuria in normal range so we did not perform other tests for Sarcoidosis.

Parameters	Values		Units	Reference range
pH	7.33	7.4		7.35-7.45
pCO ²	2.8	1.2	kPa	4.3-5.7
pO ²	15.2	22.5	kPa	9.5-13.5
HCO ³ (-)	11.1	8.7	mmol/l	21-28
HCO ³ std	14.8	13.6	mmol/l	22-26
TCO ²	11.7	9.1	mmol/l	22-29
BE ect	-14.8	-16.1	mmol/l	-2-3
BE (B)	-13	-14.6	mmol/l	-2-3
sO ²	98.10%	99.50%	%	94-98

Table 3: Review of acid-base balance during hospitalization.

She was controlled by a neurologist. The EMNG (electromyoneurography) was done and it pointed at sensomotoric and primarily demyelinating polyneuropathy with mild symptoms. There were no myopathy changes. In further treatment, an EGDS (esophagogastroduodenoscopy) and mucosal biopsy taken from antrum and corpus ventriculi have been done. Pathohistological findings showed chronic active bacterial gastritis. Fecal occult blood test was negative. Except the micro calcification in the left kidney, abdominal CT scan (computerized tomography scan) was with no pathological changes. Adrenal glands MRI (magnetic resonance imaging) test have been done and it described adrenal glands of appropriate morphological and MRI tissue's characteristics. The biopsy of salivary glands was send to the revision.

The treatment at our department started with potassium substitution therapy and high dose corticosteroid therapy with tapering. Bicarbonates were including due to the presence of metabolic acidosis. After the implementation of the therapy, there was an improvement of the patient's condition in general. On several occasions an endocrinologist was consulted about corrections in the treatment of metabolic acidosis and hypokalemia. Gradually a significant improvement in the patient's condition was detected and also the stabilization of the potassium level in her blood and her acid base status, the patient was capable to walk alone. She was discharged from the hospital in generally good condition, hemodynamically stable for further ambulatory care with the substitution treatment by potassium's and bicarbonate's preparations. In the further therapy, antimalarial medications and corticosteroids maintained. The 24 h patient's sample of urine and the sediment were normal and with no elements of glomerulonephritis and without lung disease there was no need for conventional immunosuppressive treatment.

Conclusion

A 35 years old female patient, with a clinical presentation of severe hypokalemia (at ER potassium level was 1.5 mmol/l) and metabolic acidosis with the possible Sjögren syndrome, did not have enough elements for the final diagnosis of the disease. Considering the presence of subjective criteria, expressed Sicca syndrome, highly

positive immunology anti Ro At (SS/A) and anti La At (SS/B) and a biopsy that did not provide enough data, we could assume on presence of Sjögren syndrome. To determine the final diagnosis, the extra glandular manifestations were very useful, the status of kidney and the presence of distal renal tubular acidosis. Metabolic acidosis and hypokalemia with regular anion gap in the presence of positive immunology and sicca symptoms approved enough data to make a diagnosis of RTA type 1. In the literature we can find many similar examples. In PubMed Central[®] (PMC), a free archive of biomedical and life sciences journal literature for example, we founded the case of a patient with a hypokalemia as a primary manifestation of Sjögren syndrome with a reference to similar cases. There were reported 52 cases of hypokalemic paralysis in Sjögren syndrome patients, and in some cases, distal renal tubular acidosis was present before the diagnosis of primary Sjögren syndrome (pSS) [7]. It must be emphasized that the underlying problem in distal renal tubular acidosis is a reduced excretion of H⁺ ion in the distal part of the nephron. Distal renal tubular acidosis is usually associated with inadequate high urine pH values (usually >5.5), decreased renal acid excretion, and urinary excretion of bicarbonate. Hyperchlormic metabolic acidosis with normal anionic gap, along with a hypokalemia, usually is a consequence of distal renal tubular acidosis. Renal tubular acidosis type 1 is usually accompanied by urinary sodium loss, which then cause a secondary hyperaldosteronism and a loss of kalium through the urine. There are several causes of distal renal acidosis and one of them is exactly autoimmune diseases like Sjögren's syndrome [8]. The consequence of hypokalemia leads to weakness, numbness, muscle cramps, and in severe cases to paralysis, as it was the case with our patient. Long term complications include osteomalacia and kidney stones. After correction of metabolic acidosis and plasma's potassium values, the stabilization of the patient's general condition was observed, the return of muscular strength and the possibility of walking without help.

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