Sicca syndrome and autoimmune central diabetes insipidus: a case report

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Abstract

The authors describe a case of a 67 year old woman with a history of Paget's disease of the bone, presenting Sicca Syndrome, of unknown etiology, for which she was admitted to the hospital Internal Medicine department. A clinical discussion resulted in several possible differential diagnoses. After undergoing several tests, a final diagnosis of Central Diabetes Insipidus of autoimmune etiology was reached.

Key words: Sicca syndrome, xerophalmia, xerostomia, Paget's disease of the bone, central diabetes insipidus.

INTRODUCTION

Sicca syndrome, also known as keratoconjunctivitis sicca, is characterized by reduced tear formation (xerophthalmia) and decreased saliva production (xerostomia). It is associated with diseases of different etiologies, including autoimmune, neoplastic, endocrine, infectious and rheumatologic diseases.[1] This syndrome may be a form of presentation of diabetes insipidus, a rare endocrinological disease with prevalence of 1 case in 25,000 in the U.S.A, equal incidence for both sexes, and occurring at any age.[2] The distinguishing characteristic of the disease is the inability of the kidney to concentrate the urine, resulting in low urine osmolality.[3]

CLINICAL CASE

Female patient, 67 years of age, Caucasian, with a previous history of gallstones, Paget's bone disease diagnosed ten years earlier, and a right hip joint prosthesis nine years earlier. She had no history of cranioencephalic trauma or neurosurgery. A family history of breast cancer (mother), colon neoplasm (brother), leukemia (aunt), cerebrovascular accident (CVA) (father), pulmonary thromboembolism (brother) and chronic renal insufficiency (sister). She had taken no medication as an outpatient.

Apparently without complaints until one month previously, when she began to experience dysphagia for solid foods, associated with regurgitation and epigastric pain, without signs of either relief or worsening, and heartburn. She also showed signs of xerophthalmia and xerostomia, polydipsia, polyuria, nocturia, slight weight loss, anorexia and asthenia. She had no polyphagia, odynophagia, high temperature, dysuria, pollakiuria, or changes in bowel habits. She was treated with metoclopramide by her doctor, but with no benefit, and was therefore referred to our hospital.

On physical examination, the patient was obese but in good general health, conscious and cooperative, skin and mucosa with good color, dehydrated, marked xerophthalmia and xerostomia, tongue showing atrophy of the papillae on the underside and absence of saliva. She was admitted to the Medicine Service I for clinical study.

The results of the complementary diagnostic tests were as follows: high sedimentation rate (73 mm/1h); Hypernatremia (162.0 mmol/L), Hyperchloremia (139.0 mmol/L), hypocalcaemia (8.2 mg/dl) and hypophosphataemia (2.5 mg/dl). Creatinine clearance was slightly decreased (44.6 ml/min) and urinary osmolality extremely low (87.5 mOsm/Kg). Protein electrophoresis showed mild hypoalbuminaemia, with increased alpha-1 and alpha-2 fractions, biclonal increase in beta fraction, and gamma fraction unchanged. Negative viral serologies (HIV 1 and 2, HBV, HCV, and VDRL) and normal immunological markers (ANCA, ENA's, ANTI-DNA, RA). Of the tumor markers, an increase in beta 2-microglobulin (2657.70 µg/L) is highlighted, with the remaining markers (CEA, CA 19-9, CA 15-3 and CA 125) sho-

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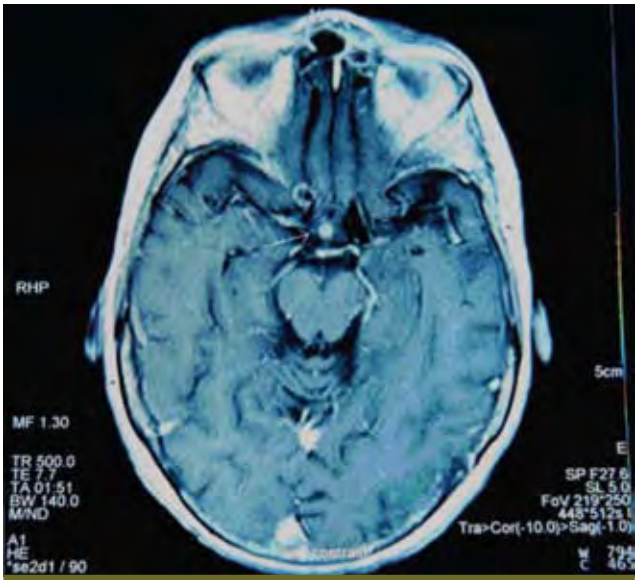
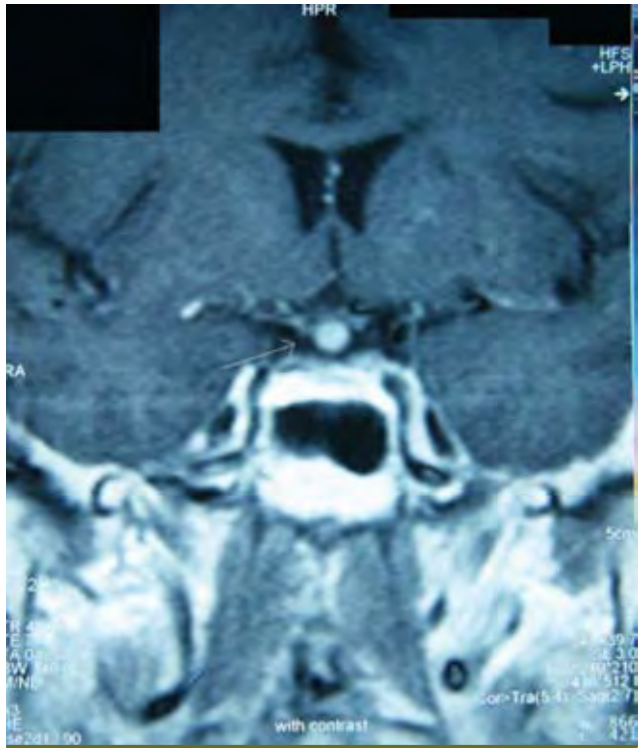


Figure 1. MRI - CE, sagittal section with contrast. The white arrow indicates the thickened hypophyseal stalk, with homogeneous and intense contrast solute enhancement.

FIG. 1



MRI - CE, transverse section with contrast. The white arrow indicates the hypophyseal stalk, with homogeneous and intense contrast solution enhancement

FIG. 2

wing no change.

Chest x-ray showed an increase in diameter of the aortic arch and thoracic aorta, and x-ray of the long and axial bones showed the presence of a left coxofemoral prosthesis, with no further changes. An esophageal transit test was requested, which showed no alterations in the progression of the contrast column, with deviation of the esophagus to the right due to aortic ectasia; upper gastrointestinal endoscopy (EGD) showed a sliding hiatus hernia, bile reflux gastritis and endoscopic erythematous-exudative gastritis. Computed Tomography (CT) of the chest, abdomen, and pelvis was performed, showing a prominence in the aorta, but with no pathological features, signs of gallstones, and slightly enlarged uterus with gross calcifications suggestive of calcified fibroids, and no ileopelvic adenopathies.

Ultrasound scan of the parotid and submaxillary salivary glands showed preserved morphology, with no focal or diffuse changes in the echo structure, and absence of intra-or peri-glandular calcifications or submaxillary or submentonian adenopathies.

Cranioencephalic Magnetic Resonance (MR) *(Figs. 1 and 2)* revealed a lesion with enlargement of the pituitary stalk, a possible differential diagnosis being a secondary neoplastic deposit or infiltration due to a hemopathy.

A Schirmer test was also performed, which confirmed lacrimal hyposecretion, with progression on the filter-paper <0.5 mm, BUT <5 seconds, and the water deprivation test *(Table 1)*.

DISCUSSION

Given the clinical picture of progressive polydipsia, polyuria, xerophthalmia and xerostomia, and dysphagia to solids, in a woman aged 67 years, we had to consider several possible diagnoses.

The most frequent cause of polyuria-polydipsia is diabetes mellitus, common in obese middle-aged patients, with decreased insulin production, insulin resistance or increased glucose production. Clinically, the classic triad consisting of polydipsia, polyuria and polyphagia is prominent, accompanied by weight loss.[4] In favor of this diagnosis, the patient reported polydipsia, polyuria and mild weight loss; nevertheless the assessment of glycaemia on several occasions was within the normal blood glucose range, excluding

Table I

Water deprivation test

	Clinical Symptoms	BP (mmHg)	Pulse (bpm)	Weight (Kg)	Urine Macro. Notes	Vol. Urine (ml)	Density	Urine Osm. (mOsmol/ Kg)	Plasma Osm. (mOsmol/Kg)
Before the test	Skin and mucosa good color and hydrated. No skin folds.	159/87	92	82.2	Color: pale yellow. Clear.		1.001	87.5	290.908
1st hour	Skin and mucosa good color and hydrated. No skin folds.	146/82	96	82.0	Color: pale yellow. Clear.	265	1.001	97.1	
2nd hour	Mentioned thirst. Skin and mucosa good color and hydrated. No skin folds.	157/86	102	81.4	Color: pale yellow. Clear.	160	1.001	104.6	298.18
3rd hour	Thirsty. Skin and mucosa good color and hydrated. Skin folds present.	145/85	107	82	Color: pale yellow. Clear.	165	1.001	104.6	
4th hour	Thirsty. Skin and mucosa good color and hydrated. Skin folds present.	147/92	109	80.9	Color: pale yellow. Clear.	165	1.001	100.69	300.32
5th hour	Skin and mucosa good color and hydrated. Skin folds present.	141/74	116	81.8	Color: pale yellow. Clear.	120	1.002	150.4	299.176
6th hour	Skin and mucosa good color and hydrated. No skin folds.	147/82	104	81.9	Color: pale yellow. Clear.	60	1.004	260.0	
7th hour	Improved mucosa hydrated	145/84	99	82.4	Color: pale yellow. Clear.	50	1.006	363.3	292.856
8th hour	Improved hydration of the mucosa	139/79	96	82.4	Color: pale yellow. Clear.	30	1.008	483.7	

Remark: The test was interrupted after the 4 th hour, due to an increase in plasma Osmolality above 300 mOsmol/Kg.
The plasmatic and urinary Osmolality was calculated using the following formula: K1 (Sodium) + K2 (Glucose) + K3 (Urea) + 9, where K1, K2 and K3 are constants with the following values 1.86; 0.056 and 0,36, respectively.
Rmks: Clinical – Clinical observations; BP – Blood Pressure; Rmks Urine Macro. – Urine macroscopy observation; Vol. Urine. – Volume of Urine; Urine Osm. – Urinary Osmolality; Plasma Osm.– Plasma Osmolality.

Table II

Common Causes of Polyuria

Category	Mechanism	Examples
Polyuria Sensitive to ADH	Reduction in ADH secretion	Primary Central Diabetes Insipidus
		Secondary Central Diabetes Insipidus
	Reduction in ADH liberated	Psychogenic polydipsia
Polyuria Resistant to ADH	Renal resistance	Congenital Nephrogenic Diabetes Insipidus
		Secondary Nephrogenic Diabetes Insipidus
	Osmotic Diuresis	Hyperglycemia Non-reabsorbed solutes: urea, mannitol, sorbitol.

this hypothesis.

Another frequent cause of clinical symptoms of polyuria-polydipsia is diabetes insipidus. This endocrinal disease is subdivided into central diabetes insipidus, when it is due to a decrease in ADH (Anti-Diuretic Hormone) secretion, and in the case of renal resistance to ADH action, nephrogenic diabetes insipidus.[3] ADH is produced in the hypothalamus, and is the main determining factor of free water excretion through its action at the renal level, as it alters the permeability of cortical and medullary collecting duct, through at least two receptors.[2]

In the majority of cases, central diabetes insipidus (CDI) is idiopathic,[3] but may also be secondary to various pathological processes, such as a head injury (particularly of the base), neurosurgery, pituitary tumor, metastasis (cancer of the breast and lung), Hand-Schuller-Christian disease, granulomas (sarcoidosis; tuberculosis), vascular lesions (aneurysms; thrombosis) and infection (encephalitis; meningitis).[5]

In the case of nephrogenic diabetes insipidus, the cause, in the majority of cases, is genetic, linked to the X chromosome. It may also be provoked by a change in the renal collecting duct or medulla, making the kidney insensitive to the action of ADH, as is the case with polycystic renal disease, pyelonephritis, hypokalemia, hypercalcemia, amyloidosis, Sjögren syndrome, myeloma or nephrotoxins (e.g. lithium).[6]

Diabetes insipidus can occur at any age, progressing gradually or quickly. Clinically, patients develop polyuria (3 to 20 L/day), polydipsia and nocturia, often resulting in dehydration.[3] Generally there is low urine osmolality, and hypernatremia may occur when the patient is unable to replace lost water.[5] In central diabetes insipidus, changes in the pituitary stalk are frequent, with enlargement that can be observed in the MRI-CE.[7]

The differential diagnosis of diabetes insipidus should include the causes of polyuria *(Table II)*[5] and hypernatremia *(Table III)*.[8] Psychogenic polydipsia, an emotional disturbance, is highlighted, where there is no organic cause of polydipsia. Unlike what happens in diabetes insipidus, patients with psychogenic polydipsia do not have nocturia, or wake up thirsty during the night. They may drink up to six liters of water per day, which if not corrected, may cause acute hyponatremic encephalopathy.[3]

The water deprivation test confirms the diagnosis and enables a differentiation to be made between the two types of diabetes insipidus and excludes the diagnosis of psychogenic polydipsia. This measures the maximum capacity to concentrate urine and the response to exogenous ADH. In central diabetes insipidus, after administration of vasopressin or desmopressin (pharmaceutical forms of ADH), urine osmolality increases by 50-100% within two hours, while in nephrogenic diabetes insipidus, there is only a slight increase in urine osmolality (<50 mOsm/kg).[3,9]

In favor of the diagnosis of diabetes insipidus, the patient reported clinical signs of polyuria, polydipsia and nocturia, as well as being dehydrated. Laboratory tests showed reduced urine osmolality. The water deprivation test *(Table I)* confirmed the diagnosis of central diabetes insipidus, with a significant increase in urinary osmolality after administration of vasopressin, supporting the diagnosis of central diabetes insipidus. As for the etiological diagnosis, after exclusion based on clinical findings and complementary diagnostic procedures, the diagnosis arrived at was idiopathic central diabetes insipidus.

Where there are progressive clinical signs of xerostomia and xerophthalmia, we also considered primary and secondary Sjögren syndrome.

Table III

Etiology of Hypernatremia

1. Water loss not replaced	
A. Insensitive losses	1. Increased sweating: temperature; exposure to high temperatures; exercise. 2. Burns 3. Respiratory infections
B. Gastrointestinal losses	1. Vomiting 2. Osmotic Diarrhea: lactulose, malabsorption, some infectious enteritis
C. Renal losses	1. Central Diabetes Insipidus a) Idiopathic b) Secondary: e.g. trauma, neoplasm, granulomatous or infectious diseases. 2. Nephrogenic Diabetes Insipidus a) Insensitivity to ADH 1. Congenital 2. Secondary: e.g. drugs, hypercalcemia, hypokalemia. b) Interference from the countercurrent mechanism 1. Osmotic diuresis: glucose, mannitol, urea 2. Loop diuretics 3. Acute and chronic renal failure 4. Hypercalcemia, Hypokalemia. 5. Sickle cell anemia
D. Hypothalamic Dysfunction	1. Primary Hypodipsia 2. Essential hypernatremia
E. Water loss from inside cells	1. Intense Exercise 2. Convulsions 3. Rhabdomyolysis
2. Sodium Gains	
A. Sodium or sea water intake	
B. Infusion of hypertonic sodium chloride or sodium bicarbonate	
C. Hypertonic enteral feeding, hypertonic enemas, or emetics	
D. Hypertonic dialysis	
E. Primary hyperaldosteronism, Cushing's syndrome	

Primary Sjögren syndrome, a progressive autoimmune disease, mainly affects middle aged female patients, with xerophthalmia as the predominant symptom. It is the result of lymphocyte infiltration from the exocrine glands, leading to their enlargement, and hyperactivity of the B lymphocytes, demonstrated by the presence of autoantibodies (rheumatoid factor) and nuclear and cytoplasmic antigens (Ro/SS-A and La/SS-B).[1]

Sjögren syndrome may be secondary to various autoimmune diseases such as rheumatoid arthritis, lupus, or vasculitis of the small and medium arteries,[1] dermatomyositis and polymyositis, Hashimoto thyroiditis, Lymphocytic interstitial pneumonia, thrombocytopenic purpura, and other diseases such as Waldenstrom's Macroglobulinemia and interstitial nephritis.[10]

In terms of clinical symptoms, Sjögren syndrome is characterized by a reduction in secretion from the exocrine glands, affecting mainly the salivary and lacrimal glands, confirmed by sialometry, sialography and the Schirmer test. The absence of saliva can result in dysphagia for solids and regurgitation.[9] The definitive diagnosis is obtained by a biopsy of the

salivary glands, showing the presence of infiltrating lymphocytes.[9]

In favor of the diagnosis of Sjögren syndrome, the patient reported xerostomia and xerophthalmia, which was confirmed by the Schirmer test, and the presence of dysphagia for solids. However an echography of the parotid glands showed normal sized glands. The absence of suggestive clinical symptoms, i.e. analytical alterations, namely auto antibodies (rheumatoid factor) and nuclear and cytoplasmic antigens (Ro/SS-A and La/SS-B) made Sjögren syndrome unlikely.

It was also necessary to exclude other causes associated with sicca syndrome. These include autoimmune diseases (lupus, scleroderma, rheumatoid arthritis and primary biliary cirrhosis), infectious diseases (HIV, HBV and HCV), cancer (lymphoma),[1] medication-related causes (oral contraceptives, antihistamines, beta blockers and phenothiazines) and a vitamin A deficit.[6,10]

We considered the possibility of neoplasia, associated with a paraneoplastic syndrome, supported by the patient's family history. Of these, the most likely was an esophageal neoplasm, which would explain the dysphagia for solid foods,[11] an osteosarcoma, a common complication of Paget's disease of the bone, a lymphoma associated with Sjögren syndrome, or an occult neoplasm, not visible on the imaging findings.

CONCLUSION

Based on the clinical symptoms and the results of the complementary diagnostic tests, Central Diabetes Insipidus associated with Sicca syndrome of autoimmune cause was the diagnosis reached, after excluding infectious, neoplastic and rheumatic causes.

Due to the absence of ADH, the patient is not concentrating urine, a fact demonstrated by the low osmolality of the urine, resulting in severe dehydration with resulting xerophthalmia, as evidenced by the Schirmer test, xerostomia and dysphagia for solids, and analytically in hypernatremia and hyperchloremia. The definitive diagnosis was ultimately decided by the water deprivation test.[3,10]

The changes in the protein electrophoresis support an autoimmune etiology, as well as the increase of β2-microglobulin isolate, as this represents the light chain of class I histocompatibility antigens (HLA).[13] Radiologically, a lesion with expansive characteristics of pituitary stem in the MRI-CE is a common finding in patients with central diabetes insipidus.[7]

Central diabetes insipidus is treated by the administration of intranasal Desmopressin (100 mcg/ml/day or every 12 hours), or orally (0.1-0.2 mg, maximum 0.4 mg every 8 hours) in an attempt to replace the ADH, with good results. In the case of nephrogenic diabetes insipidus, treatment is more difficult. The main therapeutic approach is the use of diuretics of the thiazide group (such as hydrochlorothiazide 25 mg/day or every 12 hours), and NSAIDs such as ibuprofen and indomethacin, which cause a decrease in urine volume on interacting with ADH-sensitive sites in the renal collecting ducts, increasing the sensitivity of the ADH renal receptors.[2]

The patient is currently being treated with intranasal desmopressin, with a complete reversal of the clinical condition. ■

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