Inappropriate antidiuretic hormone secretion

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Abstract

We report a case of schizophrenia associated to syndrome of inappropriate secretion of antidiuretic hormone. Clinical and laboratorial signs are discussed, emphasizing aetiologic factors associated with this syndrome.

Recent studies have shown that hyponatraemia in chronic patients can be explained by two main mechanisms: potomania and/or syndrome of inappropriate secretion of ADH.

Hyponatraemic encephalopathy was first described by Rowntree in 1923. It is characterized by: headaches, blurred vision, weakness, cramps, salivation, vomiting, diarrhoea, seizures and coma.

We describe a schizophrenic patient with multiple potential causes of hyponatraemia such as primary polydipsia and the syndrome of inappropriate secretion of antidiuretic hormone induced by psychotropic drugs – neuroleptics – and smoking. His situation improved with isotonic saline infusion and water restriction although he remained on small doses of neuroleptics.

Key words: syndrome of inappropriate secretion of antidiuretic hormone, hyponatraemia, schizophrenia, neuroleptics.

Introduction

The purpose of this article is to provide a warning on the importance of recognizing a clinical entity that has been given scant attention in patients admitted to the wards of the Internal Medicine Services: syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Syndrome of episodic water intoxication by polydipsia with excessive ingestion of water is a clinical entity that occurs almost exclusively in patients with chronic mental illnesses – a situation known as PIP (psychosis, intermittent hyponatraemia and polydipsia).[1,2] Given that excessive water ingestion is not, in itself, sufficient to produce severe hyponatraemia, it is postulated that there is another associated condition, and it has been observed that the most common is inadequate secretion of antidiuretic hormone.[3,4,5]

Of the chronic mental diseases, schizophrenia is the one in which potomania and water intoxication are most frequently observed.

Once recognized, hyponatraemia is easy to treat, and the prognosis is generally good, depending on the etiology, severity of encephalopathy, age, and sex.[6]

In the clinical case present here, a schizophrenic patient in decompensation of his mental condition, potomania associated with a neuroleptic drug contributed to significant hyponatraemia, which led to severe alterations in consciousness leading to hospital admission.

Case report

Male, aged 49 years, White, suffering from schizophrenia since the age of 22, with various outbreaks and some episodes of hospitalization in psychiatric institutions, and intercritical periods without symptoms, lasting several years.

Six months before the present hospitalization, he experienced deliriums, hallucinations, and total insomnia, and it is not known whether he complied with the prescribed medication - Flupentixol, a thioxanthene in injectable depot form, monthly, Diazepam and Biperiden "per os", daily – without psychiatric follow-up since that time. Since then, particularly over the last two months, he has drunk water compulsively – primary or psychogenic polydipsia ¾ with a consequent increase in diuresis.

Smoking history of 15 pack-years.

The patient was independent until the date of admission, when he had a convulsive crisis, vomiting, loss of control of the sphincters, lethargy and intense prostration, with disturbances in state of consciousness leading to hospitalization.

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The initial observation showed: pyknic habit; vitiligo affecting the hands and feet; hair distribution according to sex and age. No edemas. Normal skin temperature, with turgor and elasticity maintained. Mucosa normal color and hydrated.

He was confused and did not obey simple orders. He had blood pressure of 130/80 mm Hg with central heart rate of 72 bpm, rhythmic and regular, with strong radial pulse. Cardiopulmonary and abdominal observation did not show any alterations.

Pupils isocoric and normally reactive to light; fundoscopy showed no evidence of stasis or retinopathy. No nystagmus. No dysfunction of the cranial pairs. No meningeal signs. No asymmetry of strength or muscle tone in the four limbs. Osteotendinous reflexes present and symmetrical. Plantar reflexes in plantar flexion. It was not possible to test the tactile, thermal or pain sensitivities.

The following are highlighted from the analyses performed on admission:

Serum biochemistry: sodium 113 mmol/L, chlorides 76 mmol/L, potassium 3.9 mEq/L, urea 19.2 mg/dl and creatinine 0.39 mg/dl. The serum osmolality was 227 mOsm/Kg.

In the hemogram: Hb 13 g/dL, leukocytes 16,900 with 87% neutrophils. The coagulation parameters were normal. The serum benzodiazepine assay was positive.

The serum levels of FT3, FT4, T3, T4, TSH and cortisol were normal. Type II urine showed: density 1010, pH 8, without proteinuria, without ketone bodies; urinary sediment showed some erythrocytes. Urinary osmolality was 418 mOsm/Kg, with urinary sodium of 92 mEq/L.

ECG did not show any alterations. Teleradiography of the chest was normal. Cranial CT scan showed only diffuse clusters of cortical sulci of the cerebral convexity. Cranial MRI showed: punctiform hyper signals in the basal ganglia/deep gray matter, and a rounded hyper signal of slightly larger dimensions, located in the left subcortical parietal white matter, compatible with dilation of the Virchow-Robin space, retrospectively, and a small focus of demyelinization of vascular cause. Dilation of the sulci of the cerebral convexity, causing cortical atrophy. Renal echography showed kidneys of preserved dimensions, with clear corticomedullary differentiation and no pyelocalyceal dilation.

The patient was medicated with isotonic sodium chloride, at a rate of 0.5 mmol/L/hour. After around 24 hours, the patient had sodium 130 mmol/L, chloride 94 mmol/L and potassium 3.9 mEq/L. The leukocyte count was 13,800 with 87% neutrophils.

The patient recovered consciousness, with normalization of natraemia, remaining collaborative, but with psychotic mental deterioration, echolalia, laughing for no apparent reason, and poor speech.

Medicated with Haloperidol (12.5 mg/day), Biperiden (4 mg/day) and Diazepam (5mg/day), with improvement in his mental state.

The diuresis, which was initially 2,200 ml, decreased to a mean value of 700ml per day, with the patient remaining on restricted free water consumption of around 600 to 800 ml per day. Urinary ionogram on the fifth day of hospitalization showed natriuria of 15 mEq/L and kaliuria of 27 mEq/L (normal values), with hypochloruria of 16 mEq/L. Urinary osmolality was changed to 310 mOsm/Kg (ref. value 300 to 900).

Discussion

The hypothalamus, and in particular the supraoptic nuclei (which sends projected images to the cortex, amygdala and cerebral trunk) are responsible for the secretion of ADH and may have a role in both psychiatric disease and electrolyte regulation.[3] In schizophrenia, there is an increase in dopaminergic activity in the limbic structures.[5]

The antidiuretic hormone (ADH) or vasopressin, is segregated by the supraoptic and paraventricular nuclei of the anterior hypothalamus, and stored in the neurohypophysis.[8,9] The ADH binds to a receptor of the distal tubes and collector, facilitating the hydro-osmotic flow of water from the tubular lumen to the tubulointerstitium.[2,9]

The 2% increase in osmolality of the extracellular liquid stimulates the osmoreceptor cells located in the CNS (hypothalamus) to segregate ADH and angiotensin II, and stimulates the thirst center.[8,9]

Table I shows the substances and situations that stimulate and inhibit the secretion of ADH.

The most frequent etiologies of SIADH or Schwartz-Bartter syndrome are shown in Table II.[8,10]

The main characteristics of SIADH are as follows:
1. normovolaemia or expansion of plasma volume without peripheral edema, which rules out the existence of sodium deficit as the cause of hyponatraemia; extracellular hypotonicity causes intracellular edema.
2. natriuresis - the urinary Na+ concentration is hi-

TABLE I

Agents interfering in ADH secretion

Stimulate	Inhibit
b-Adrenergic antagonists	a-Adrenergic antagonists
Angiotensin II	Alcohol
Barbiturates	diphenyl-hydantoin
Carbamazepine	Atrial natriuretic peptide
Cyclophosphamide	
Clofibrate	
Hypoxia and hypercapnia	
Metoclopramide	
Morphine and analog opiates	
Nicotine	
Prostaglandin E2	
Thiazides	
Vincristine	

gher than 40 mmol/L; the expansion of volume results in an increase in atriopeptin secretion (atrial natriuretic peptide), which increases glomerular filtration and inhibits the absorption of tubular sodium. There is suppression of the renin-angiotensin-aldosterone system secondary to normo/hypervolaemia.[7,11]

3. urinary osmolality higher than 300 mOsm/Kg, manifested as urine that is not maximally diluted.

4. lowering of plasma osmolality, which rules out pseudo-hyponatraemia.

The patient presented in this case study was referred to the Emergency Service of Santa Maria Hospital due to deterioration of consciousness, as a result of severe hyponatraemia (less than 120 mEq/L) which manifested as: convulsions, vomiting, lethargy, drowsiness and coma.

The patient was medicated in the outpatient clinic with neuroleptic, antiparkinsonian and benzodiazepine, for schizophrenia with around seventeen years of evolution. Characteristically, serum Na+ and osmolality were decreased, as well as serum uric acid. The urinary osmolality was higher than that of the serum. The urinary Na+ was higher than 30 mEq/L and the FeNa+ was higher than 1%. Cranial-encephalic MRI did not show the image characteristically associated with SIADH, which is the absence of normal hyper signal corresponding to neurohypophysis.[12] However, the cerebral lesion that most commonly occurs in

TABLE II

Malignant neoplasias

Head and neck, bronchogenic, pancreatic, duodenal, vesical, and prostate carcinomas

Lymphosarcomas and Hodgkin's disease

Timoma e mesotelioma

Pulmonary diseases

Tuberculosis, aspergillosis

Lung abscess, empiema, bacterial pneumonias

Pneumocystis carinii pneumonia (PCP) in patients infected by HIV

Ventilation with positive pressure

Asthma, COPD, pneumothorax

Diseases of the Central Nervous System

Skull fractures

Subdural haematoma, subarachnoid hemorrhage

Acute meningitis and tuberculous meningitis, thrombosis of the cavernous sinus

Guillain-Barré Syndrome

Olfactory neuroblastoma, hydrocephalus

Other diseases

Acute intermittent porphyria

Systemic erythematous lupus

Giant cell arthritis

Antiphospholipid syndrome

Infection by the HVZ virus in patients infected by HIV

Hypothyroidism

Malaria by *P. falciparum*

Respiration by positive pressure

Drugs

Thioridazine, amitriptyline, fluoxetine, sertraline, thioridazine, desipramine, haloperidol, chlorpromazine, carbamazepine, valproate, morphine, vidarabine, vincristine, cyclophosphamide, chlorhydrate, oxytoxin, isoproterenol, diclofenac and thiazides.

(Chronic administration of neuroleptics increases the reactivity of the secretory response to vasopressin)

hyponatraemic encephalopathy is the result of cerebral edema and increased intercranial pressure, as a result of the decreased flow and cerebral hypoxia, manifested by cerebral strokes, shown in the patient presented here, through the cranial MRI.[6]

By restricting the ingestion of water to 600 to 800

ml per day, the patient lost around 2 Kg in weight in the first 2 to 3 days, and hyponatraemia was corrected.

In these situations, the hyponatraemia should be corrected gradually, at a rate of 0.5 mEq of Na+/L/hour up to 120 to 125 mEq of serum sodium, after which it may be corrected more quickly.

The sudden increase in sodium to values higher than 120 or 125 mEq/L may lead to a CNS injury known as central pontine myelinolysis, which consists of demyelinization of the fibers, manifested as: flaccid quadriplegic or paraplegic paralysis, dysphagia, dysarthria and coma. This injury is more common among malnourished, alcoholic patients.[13,14]

In SIADH, isotonic sodium chloride should be administered, associated with furosemide. Diuretics induce a loss of salt reducing the risk of expansion of extracellular volume.[15,16]

In chronic cases SIADH, and in acute situations without response to water restriction, demeclocycline can be administered, an antagonist tetracycline of the effects of ADH in the distal and collecting tubules.[17]

Once the drug involved in the SIADH has been identified, this should be suspended when possible.[18] In the case of the patient presented, it was necessary to maintain a neuroleptic drug, haloperidol, for control of his chronic psychiatric disease, however making possible to return serum sodium to its normal levels, highlighting the intake contribution whilst triggering the condition. ■

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