MECHANISMS OF HYPONATRAEMIA IN ALCOHOL PATIENTS

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Abstract — Hyponatraemia is commonly reported in chronic alcoholic patients. However, the underlying pathogenetic mechanisms are not well delineated. In the current study, we analysed the possible pathophysiological mechanisms of hyponatraemia in a group of alcoholic patients ($n = 127$) admitted to our hospital for causes related to alcohol misuse. Hyponatraemia (serum sodium <134 mmol/l) was found in 22 patients (17.3%). The most common cause of hyponatraemia in our cohort was hypovolaemia (12 patients); pseudo-hyponatraemia was diagnosed in six patients with alcohol-induced severe hypertriglyceridaemia. It is of interest that two patients fulfilled the criteria of the so-called 'beer potomania' syndrome, while in two others, hyponatraemia was due to reset osmostat or to cerebral salt wasting syndrome, not previously described in alcoholic patients. It is concluded that hyponatraemia is a frequently observed electrolyte disorder in hospitalized alcoholic patients and is related to various pathophysiological mechanisms.

INTRODUCTION

Among electrolyte abnormalities observed in chronic alcoholic patients, hyponatraemia is relatively common (Kaysen and North, 1984; Schaefer *et al.*, 1987; Elisaf *et al.*, 1994). However, the prevalence of hyponatraemia and its underlying pathophysiological mechanisms in these patients are not well delineated. In the current study, we attempted to illuminate the responsible pathogenetic mechanisms of hyponatraemia in a group of alcoholic patients admitted to our hospital for causes related to alcohol misuse.

MATERIALS AND METHODS

We prospectively studied 127 out of 241 consecutive chronic alcoholic patients (120 males and 7 females) aged 29–78 years admitted to our hospital for causes related to alcohol misuse over a period of 5 years. To be eligible, the patients had to have had a large intake of alcohol for at least 5 years, and a weekly alcohol consumption of 600 g or more for the previous 3 months. The main causes of the patients' admission are shown in Table 1. Patients with diabetes mellitus, renal disease (defined by previous exposure to recognized nephrotoxic drugs, abnormal urinalysis, pathological protein-uria, or creatinine clearance <80 ml/min), ascites, peripheral oedema, acute pancreatitis, chronic obstructive lung disease, recent bleeding from the gastrointestinal tract, septic shock, convulsions occurring 1 h prior to blood sampling, as well as patients consuming drugs affecting acid-base status and electrolyte parameters such as diuretics, antacids, and potassium, phosphate and magnesium supplements, were excluded from the study. In all subjects, psychiatric evaluation was performed on admission and at 1–2 weeks after discharge. There was no evidence of psychotic disorders in any of the patients included in the study.

On admission, physical examination was performed and venous blood was obtained for the determination of serum glucose, urea, uric acid, creatinine, total proteins, albumin,

Table 1. Causes of admission of patients studied ($n = 127$)

Reason	No.	%
Alcohol withdrawal syndrome	25	19.7
Increased serum liver enzymes and/or hepatomegaly	27	21.2
Acute intoxication	26	20.5
Anaemia	11	8.7
Diarrhoea	7	5.5
Chronic alcoholic pancreatitis	7	5.5
Gastrointestinal symptoms (nausea, vomiting, dyspepsia, epigastric pain)	6	4.7
Chronic myopathy	4	3.1
Peripheral neuropathy	6	4.7
Epistaxis	3	2.4
Ataxia	5	3.9

lipid parameters (total cholesterol, triglycerides), osmolality (P_{osm}), potassium, sodium, calcium, phosphorus, chloride, magnesium, and bicarbonate prior to any therapeutic intervention. Arterial blood was also obtained for blood gas measurements. At the same time, a fresh urine specimen was tested for osmolality (U_{osm}), uric acid, urea, creatinine, potassium, sodium, calcium, phosphorus, chloride, and magnesium. Standard formulae were used for the determination of the fractional excretion (FE) of electrolytes, urea, and uric acid.

In patients with hyponatraemia (serum sodium < 134 mmol/l, reference range: 136–145 mmol/l), the detection of the underlying pathogenetic mechanisms was our primary task. Diagnostic approach was based on the patients' history and their physical examination, with emphasis on extracellular volume status and on the correct interpretation of laboratory tests. The first step in this approach was to confirm the presence of hypo-osmolality ($P_{osm} < 280$ mOsm/kg) (Fig. 1). In the setting of normal or elevated effective serum osmolality [measured P_{osm} – blood urea (mg/dl)/6], evaluation of one of the causes of pseudohyponatraemia was carried out (severe hyperlipidaemia or hyperproteinaemia) (Weisberg, 1989; Rose, 1994). Once it was demonstrated that the patient was hypo-osmolar, the evaluation of the U_{osm} was used to determine whether water excretion was normal or impaired. A value of $U_{osm} < 100$ mOsm/kg was indicative of a complete and

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P_{Na}<134 mmol/l

Measure P_{osm}

Hypo-osmolar
<280 mOsm/kg

Normo- or
Hyperosmolar
≥280 mOsm/kg

Measure U_{osm}

Pseudohyponatraemia
(hyperlipidaemia,
hyperproteinaemia
etc.)

<100 mOsm/kg

Appropriate
water excretion

>100 mOsm/kg

Inappropriate
water retention

Excess fluid
consumption

Exclude thyroid and
adrenal dysfunction

Measure U_{Na}

<20 mmol/l

20–40 mmol/l

>40 mmol/l

Hypovolaemia

2 litres 0.9%
saline i.v. daily
for 2 days

Possible
SIADH
Reset osmostat
Salt wasting

Measure ΔP_{Na}

Salt supplementation
+ water restriction to
normalize P_{Na}

≥5 mmol/l

<5 mmol/l
and
U_{osm}<100 mOsm/kg
and
U_{Na}>10 mmol/l

Hypo-
volaemia

Possible reset
osmostat

Normal P_{urate}
and
reduced FE_{urate}

Reduced P_{urate}
and
unchanged FE_{urate}

SIADH
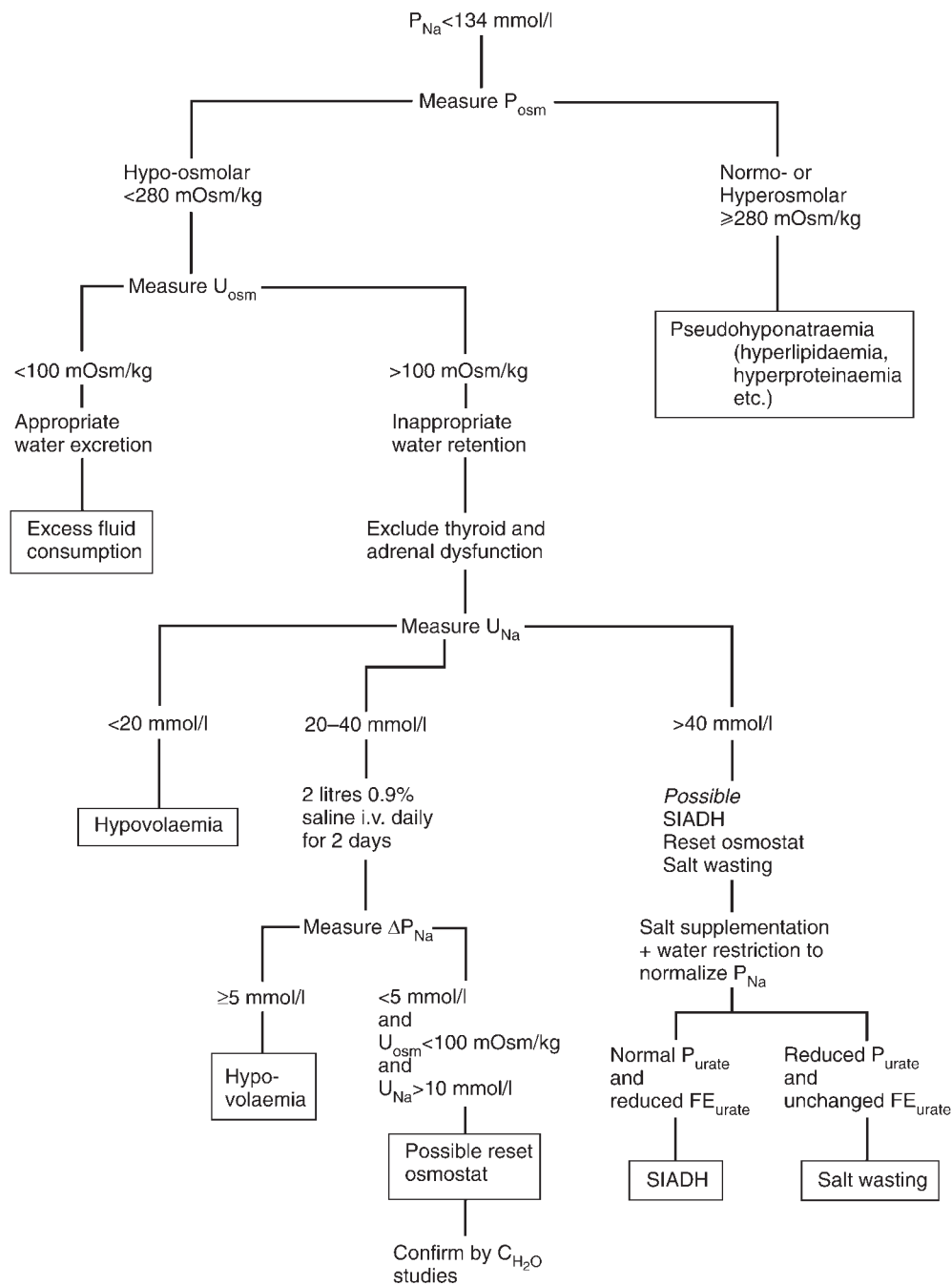
Salt wasting

Confirm by C_{H_2O}
studies

Fig. 1. Flow diagram for the diagnosis of hyponatraemia.
C_{H_2O}, free water clearance; SIADH, syndrome of inappropriate antidiuresis.

appropriate suppression of antidiuretic hormone (ADH) secretion, a finding seen with either primary polydipsia (including 'beer potomania') or reset osmostat (Gillum and Linas, 1984). The criteria used to diagnose the 'beer potomania' syndrome included a history of binge beer drinking and poor dietary intake along with decreased serum sodium levels in the absence of other known causes of hyponatraemia (Hilden and Svendsen, 1975; Fenves *et al.*, 1996). When U_{osm} exceeded 100 mOsm/kg, hyponatraemia due to impaired water excretion was diagnosed. Since patients with ascites or peripheral oedema were excluded, normovolaemic or hypovolaemic hyponatraemia

was established. In such cases, the urine sodium was evaluated in addition to assessing adrenal and thyroid function. Taking into account that patients with renal failure as well as patients receiving diuretics were excluded, a urine sodium less than 20 mmol/l was indicative of hypovolaemia, while a urine sodium greater than 40 mmol/l was suggestive of the syndrome of inappropriate antidiuresis (SIADH), reset osmostat, and of salt wasting conditions (Chung *et al.*, 1987). In patients with equivocal findings (urine sodium 20–40 mmol/l), the correct diagnosis was based on the response of serum sodium levels following the i.v. administration of sodium chloride (2 l of NaCl

0.9% w/v/day for 2 days). Hypovolaemia was diagnosed if the serum sodium concentration increased by 5 mmol/l or more as a response to this test (Chung *et al.*, 1987). The reset osmostat syndrome was suspected in patients with persistent hyponatraemia accompanied by an appropriate decrease in U_{osm} (<100 mOsm/kg) but inappropriate natriuresis (>40 mmol/l). In this setting, the diagnosis was confirmed by calculating free-water clearance (C_{H_2O}) (Defronzo *et al.*, 1976; Elisaf *et al.*, 1996). Finally, the changes of serum uric acid levels and uric acid FE were evaluated in the differential diagnosis between salt wasting syndrome and SIADH. The restoration of the serum sodium levels by salt supplementation and fluid restriction followed by a reduction in urinary urate excretion pointed to the diagnosis of SIADH, whereas the persistence of hypo-uricaemia and uric acid wasting following normalization of serum sodium levels was suggestive of salt wasting (Maesaka, 1996).

RESULTS

The acid-base and electrolyte abnormalities of the study population are shown in Table 2. Twenty-two of the 127 patients had hyponatraemia with a range of serum sodium between 121 and 133 mmol/l. However, no symptoms related to hyponatraemia were evident. The causes of hyponatraemia according to the diagnostic work-up are shown in Table 3. Thus, six patients had pseudohyponatraemia due to alcohol-induced severe hypertriglyceridaemia (serum triglycerides 2000–7200 mg/dl). A decrease in serum triglycerides was followed by the restoration of serum sodium levels in all cases. The most common cause of hyponatraemia in our cohort was hypovolaemia. In these patients, fluid loss was confirmed by history (e.g. vomiting and diarrhoea) and laboratory findings

Table 2. Acid-base and electrolyte abnormalities in the population studied (*n* = 127)

Abnormality	No.	%
Respiratory alkalosis (arterial pH > 7.46)	20	15.7
Metabolic alkalosis (arterial pH > 7.46)	7	5.5
Acidaemia[a] (arterial pH < 7.34)	14	11
Hyponatraemia (serum sodium < 134 mmol/l)	22	17.3
Hypernatraemia (serum sodium > 146 mmol/l)	3	2.3
Hypokalaemia (serum potassium < 3.4 mmol/l)	16	12.6
Hypomagnesaemia (serum magnesium < 0.65 mmol/l)	38	29.9
Hypophosphataemia (serum phosphorus < 0.77 mmol/l)	37	29.1
Hypocalcaemia (serum calcium < 2.1 mmol/l)	26 (18)[b]	20.5 (14.2)[b]
Hyperphosphataemia (serum phosphorus > 1.45 mmol/l)	2	1.6

[a]Due to either pure metabolic acidosis or to mixed acid–base disorders; [b]18 patients with true hypocalcaemia (14.2%).

Table 3. Observed causes of hyponatraemia

Cause	No.	%
Pseudohyponatraemia	6	27.3
Hypovolaemia	12	54.5
'Beer' potomania syndrome	2	9.1
Cerebral salt-wasting syndrome	1	4.5
Reset osmostat syndrome	1	4.5

suggestive of hypovolaemia, such as an increased serum urea/creatinine ratio (>40), low urine sodium concentration (<40 mmol/l), low FENa$^+$ (<0.5%) and low FE of urea (<55%) were detected. Normalization of serum sodium levels was achieved following infusion of normal saline with a greater than 5 mmol/l increase in serum sodium levels observed after a 2-day sodium chloride loading.

Two patients with serum sodium levels of 122 and 124 mmol/l, respectively, had the so-called 'beer potomania' syndrome. The patients were drinking huge quantities of beer and their diet contained very small quantities of proteins and salt. In both patients, urine sodium concentration was extremely low (<10 mmol/l), U_{osm} was appropriately low (90 and 100 mOsm/kg) and potassium levels were in the lower normal limits (3.5 and 3.6 mmol/l, respectively). In one malnourished patient with low serum albumin levels (29 g/l), the diagnosis of the reset osmostat syndrome was established. This patient had asymptomatic hyponatraemia (serum sodium 128 mmol/l) with inappropriate natriuresis (urine sodium 64 mmol/l) but appropriately low U_{osm} (95 mOsm/kg) and excreted 85% of a standard water load (20 ml/kg body weight) within 4 h. On physical examination, peripheral oedema was not present and no postural changes in blood pressure and pulse rate were evident. Thyroid, renal, liver, and adrenal function were normal. Sodium chloride administration was not followed by an increase in serum sodium levels, while sodium balance was preserved. The maximum free water clearance (C_{H_2O}) was 10.5 ml/min and did not differ from observations in previous studies on healthy individuals (reference range 5.8–15 ml/min) (Cooke *et al.*, 1979). Hyponatraemia due to cerebral salt wasting syndrome was diagnosed in a 68-year-old patient with dementia in association with alcohol-induced cerebral atrophy. Initially, the diagnosis of SIADH was made based on the coexistence of hyponatraemia (serum sodium 122 mmol/l) with inappropriate natriuresis (urine sodium 56 mmol/l) and hypouricaemia with uricosuria [serum uric acid levels 3.2 mg/dl (reference range 4–7.2 mg/dl) and FE of uric acid 18% (reference range 11–16%)]. However, the diagnosis of cerebral salt-wasting syndrome was established after a careful diagnostic follow-up. In fact, despite the natriuresis, there was evidence for volume depletion (postural hypotension). Furthermore, the correction of hyponatraemia by salt supplementation and fluid restriction was not associated with a significant rise in serum uric acid levels (serum uric acid levels 3.4 mg/dl) or a reduction in FE of uric acid (FE of uric acid 17.5%).

DISCUSSION

In the present study, the prevalence of hyponatraemia and its associated pathogenetic mechanisms were assessed in a group of hospitalized chronic alcoholic patients. In our series, hyponatraemia was the third commonest electrolyte abnormality detected (17.3%). However, in a considerable number of these patients, pseudohyponatraemia was diagnosed due to alcohol-induced hypertriglyceridaemia. In such cases, there is a marked increase in the non-aqueous phase of plasma resulting in a fall in the ratio of sodium to total volume, even though the sodium in the aqueous phase is normal and so is P_{osm} (Albrink *et al.*, 1955). True volume depletion mainly due to gastro-intestinal fluid losses represents the chief cause of hyponatraemia

in alcoholic patients. Effective volume depletion predisposes toward the development of hyponatraemia by its effects on renal water excretion and thirst. In fact, hypovolaemia is a potent stimulus to ADH secretion, resulting in water retention. Furthermore, volume depletion can directly or indirectly stimulate thirst and consequently increase water intake (Rose, 1994). The diagnosis of hypovolaemic hyponatraemia is sometimes evident from history and physical examination. However, the accuracy of clinical evaluation for predicting the state of extracellular fluid volume in hyponatraemia is low. Laboratory markers, such as the increased serum urea/creatinine ratio and the low urine sodium concentration, are particularly useful in this setting. In doubtful cases, the response of the serum sodium concentration to the i.v. administration of normal saline for 2 days is useful in establishing the correct diagnosis. An increase in serum sodium concentration greater than 5 mmol/l is indicative of hypovolaemic hyponatraemia, which was the case in all hypovolaemic patients (Chung et al., 1987). It has been proposed that the combination of low FE of sodium (<0.5%) and low FE of urea (<55%) can safely predict saline response (Musch et al., 1995). In fact, in our series, all patients with hypovolaemic hyponatraemia satisfied these diagnostic criteria. The presence of low sodium excretion in alcoholic patients strongly favours the diagnosis of hypovolaemia, since these patients commonly exhibit reversible tubular injury as a result of alcoholism and tend to increase solute excretion because of the potential diuretic effect of poorly reabsorbed substances, such as ketoacids or lactate (De Marchi et al., 1993).

The syndrome of 'beer potomania' was diagnosed in two patients. These patients were malnourished binge drinkers and presented with profound hyponatraemia. In 'beer potomania', hyponatraemia is due to a large consumption of beer (which has a poor salt content) together with a minimal intake of ordinary food. A diet poor in salt and protein compounds (i.e. urea precursors) results in reduced excretion of urinary solutes, which limits the ability to excrete free water (Hilden and Svendsen, 1975; Fenves et al., 1996; Blaustein and Schwenk, 1997). In both patients, there was an appropriate renal response to the large fluid intake by maximally diluting the urine ($U_{osm} \leq 100$ mOsm/kg). Binge drinkers typically produce less than 250 mOsm of solutes a day; hence, our patients could probably excrete no more than 2.5 l of urine daily (250/100 = 2.5 l). Since they were drinking about 3 l of beer daily, about 0.5 l of fluid was retained leading to dilutional hyponatraemia.

In one patient presenting hyponatraemia with inappropriate natriuresis, the syndrome of SIADH was implicated. However, the patient fulfilled the criteria for the diagnosis of the reset osmostat syndrome (Defronzo et al., 1976; Wall et al., 1992; Elisaf et al., 1996). Specifically, this patient had:

(1) normovolaemic hyponatraemia and could maintain sodium balance without correcting the existing hyponatraemia when sodium chloride intake was increased; (2) an intact urinary diluting ability, as his urine osmolality was lower than 100 mOsm/kg; (3) normal excretion of a standard water load (>80% within 4 h); (4) normal adrenal, renal, and thyroid function together with no evidence of cardiac or hepatic disease. Nevertheless, we cannot disregard the fact that this patient may have had a mild degree of volume depletion. Thus, ADH secretion adjusted for hypo-osmolality as well as (to some

extent) for hypovolaemia could be responsible for the patient's clinical presentation.

Hyponatraemia due to reset osmostat has not been reported in alcoholic patients. There is evidence that this syndrome is present in approximately one-third of patients with SIADH and may occur in several other conditions, including chronic malnutrition, as was the case in our patient (Defronzo et al., 1976). In this setting, defective cellular metabolism may be responsible for the abnormal osmoreceptor function. Interestingly, correction of the underlying problem and hyperalimentation were effective in returning the serum sodium concentration towards normal.

Finally, one patient with alcohol-induced cerebral atrophy and dementia presented with hyponatraemia related to cerebral salt-wasting syndrome. The diagnosis was based on a recently proposed diagnostic work-up taking into account uric acid metabolism and the patient's response to saline infusion (Maesaka, 1996). It is of interest that patients with this syndrome develop hyponatraemia with all the SIADH-associated findings (including inappropriate natriuresis and hypouricaemia). However, these patients are volume depleted and have a high urine sodium concentration due to urinary sodium wasting and not to volume expansion (Al Mufti and Arief, 1984; Ishikawa et al., 1987; Tanneau et al., 1987). The correction of hyponatraemia after saline infusion and the persistence of hypouricaemia (and inappropriate uric acid wasting) despite normalization of sodium levels suggest salt wasting (Maesaka, 1996). The cerebral salt-wasting syndrome is observed in patients with cerebral diseases and its pathogenesis remains unclear. It has been proposed that there is an increased release of natriuretic peptides from specific hormone-producing neurons in the brain stimulated by disorders of the central nervous system (Tanneau et al., 1987).

In conclusion, hyponatraemia is a frequently observed electrolyte abnormality in hospitalized chronic alcoholic patients and is related to various pathophysiological mechanisms.

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