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SCIENCE DIRECT

Clinical Biochemistry 38 (2005) 1045 – 1048

CLINICAL BIOCHEMISTRY

Case Report

Critical illness with hyponatraemia and impaired cell membrane integrity—the "sick cell syndrome" revisited

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Received 10 March 2005; received in revised form 11 July 2005; accepted 20 July 2005
Available online 25 August 2005

Abstract

Objective: To determine whether impaired cell membrane permeability exists in critically ill patients with "sick cell" type hyponatraemia.

Design and methods: A 36 year old male patient was identified in an intensive care unit (ICU) with liver disease and multi-organ failure. His initial serum sodium (Na) was 101 mmol/L and osmolar gap + 35 mmol/L. A flow cytometric system was used to assess lymphocyte membrane integrity using fluorescein diacetate (FDA) and propidium iodide (PI). Following this, similar studies were carried out in 17 hyponatraemic (Na < 130 mmol/L) and 19 normonatraemic (Na > 136 mmol/L) ICU patients.

Results: Flow cytometry in the index patient showed two clear populations of cells—one was normal (with identical characteristics to a healthy control) and the other had dysfunctional cell membrane integrity. The extended patient series, however, revealed only 2 other patients with similar flow cytometric patterns—one hyponatraemic and one normonatraemic.

Conclusions: Cell membrane studies in the index patient demonstrated supportive evidence for the "sick cell syndrome" in critically ill patients. The extended series revealed that 3/37 (8%) had this abnormality, which was however not consistently associated with hyponatraemia.

Keywords: Hyponatraemia; Sick cell syndrome; Cell membrane; Flow cytometry

Introduction

Hyponatraemia is a common biochemical abnormality [1] and may occur in many disease states and by various pathophysiological mechanisms [1–4]. Of special importance with hyponatraemia is that such patients are often significantly or even critically ill and therefore may be associated with high mortality and morbidity [3,5–7].

Well accepted causes of hyponatraemia include thiazide diuretic treatment [7], hypoadrenalism (both primary and secondary)[8], iatrogenic post-operative fluid overload [9] and the syndrome of inappropriate antidiuresis (SIAD) [10].

A further, though considerably more controversial potential mechanism of hyponatraemia in severely ill patients is the "sick cell syndrome" [11]. This concept was introduced in 1973 by Flear and Singh [11], who postulated that, in critical illness, cell membranes "leak," allowing solutes normally constrained in the intracellular fluid (ICF) to escape into the extracellular fluid (ECF). The escaping solutes are osmotically active, and cause water to move from ICF to ECF, leading to dilution of plasma sodium (Na) and consequent hyponatraemia. Sick cell hyponatraemia is usually associated with a positive osmolar gap (the difference between measured and calculated osmolality), as the "escaped osmoles" contribute to overall directly measured plasma osmolality, but not to calculated osmolality (equations for which usually assume major osmotic contributions only from sodium, potassium, urea and glucose [12]). The presence of positive osmolar gaps

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doi:10.1016/j.clinbiochem.2005.07.014

in seriously ill patients has been confirmed elsewhere [13,14] and one study suggested that amino acids were a major contribution to the "missing osmoles" [14].

The sick cell syndrome, however, has remained controversial, largely because a defect in cell membrane permeability has, to our knowledge, never been reported in association with other biochemical features of sick cell hyponatraemia. We report here a critically ill patient with severe hyponatraemia and a significantly raised osmolar gap, in whom we found flow cytometric changes suggestive of increased cell membrane permeability.

Case report

Clinical details

A 36 year old man was hospitalised with a 3 day history of malaise, drowsiness and jaundice. He had a long previous history of agoraphobia and alcohol abuse, and had undergone detoxification programmes in the past. Examination revealed an unwell looking man with moderate icterus and a fever of 38.5°C. His pulse was 100/min in sinus rhythm and blood pressure 110/60; respirations were 18/min and regular. There was no hepatomegaly, splenomegaly or lymphadenopathy. Heart and lungs were clinically normal. He was drowsy but responsive. There was no meningismus, focal neurological signs or clinical features of liver failure. An initial diagnosis was made of alcoholic liver disease and infection of an uncertain site.

Whilst investigations were proceeding, the man lost consciousness. At resuscitation, he was found to have absent respirations and an idioventricular cardiac rhythm with no recordable blood pressure. After intra-cardiac adrenaline, he developed ventricular fibrillation from which he was successfully defibrillated into sinus rhythm with output. He remained unconscious, however, with weak stertorous respirations and hypotension (BP 95/60). Two grand mal convulsions occurred. He was transferred to the intensive care unit (ICU) 6 h after original admission, and was paralysed and ventilated, and given inotropic support with dopamine. On admission to the ICU, he was not oedematous or dehydrated clinically, and his central venous pressure (CVP) was 17 cm water. Intravenous phenytoin and antibiotics (cefotaxime and metronidazole) were administered.

Investigations

Initial investigations (taken prior to the "arrest") revealed a serum sodium level (measured by an automated ion-selective electrode method) of 101 mmol/L (reference range 130–145), potassium (K) 3.6 mmol/L (range 3.5–5.0) and urea 1.4 mmol/L (range 2.5–7.5). Plasma glucose was 6.9 mmol/L (range 3.6–8.0), serum amylase 156 u/L (range 0–96), haemoglobin 12.3 g/dL (range 14.0–18.0) and chest X-ray unremarkable. With the patient breathing air, arterial blood pH was 7.22 (range 7.36–7.46), pCO_2 51 mm Hg (range 35–45), pO_2 59 mm Hg (range 75–100), base excess −6 mmol/L (range ± 2) and bicarbonate 20 mmol/L (range 21–26). Serum osmolality was 249 mosM/kg (measured by freezing point depression, range 285–295). However, calculated serum osmolality was 214 mosM/kg, with an osmolar gap of +35 mosM/kg. Urine osmolality was 260 mosM/kg (range 50–1200). Liver function tests were grossly deranged-bilirubin 197 μmol/L (range 0–20), AST 398 u/L (range 5–42) and alkaline phosphatase 136 u/L (range 30–130). Serum albumin was 28 g/L (range 36–50). Admission serum ethanol was detectable but low at 7 mg/dL. Serum cortisol was appropriately raised at 1968 nmol/L (range 140–690).

Progress

A CT brain scan was performed on the second day of admission. It showed marked generalised cerebral oedema, and an abdominal ultrasound showed only liver appearances consistent with fatty infiltration. There was a small amount of ascites. 20% mannitol, 100 mL/h, was given for 5 h and hydration was maintained with 0.9% saline with small amounts of furosemide. There was increasing oliguria, and serum creatinine rose (see Table 1). Haemofiltration was initiated on the third day when his serum creatinine was 349 μmol/L (range 0–110). Despite this, and serum Na and osmolality rising to near normal levels, the patient deteriorated. Four days after admission, metabolic acidosis occurred. Hypoxia, renal and hepatic dysfunction, and hypotension all became increasingly problematic. Dobutamine and adrenaline were added to the dopamine, and bicarbonate and mannitol infusions were used intermittently. Later on the fourth day after admission, he died. An autopsy was not performed.

Table 1
Sequential biochemical data on a patient with presumptive "sick cell" hyponatraemia

Day	Serum Na, mmol/L	Serum K, mmol/L	Serum urea, mmol/L	Serum creatinine, μmol/L	Plasma glucose, mmol/L	Measured Serum osmolality, mosM/kg	Calculated Serum osmolality, mosM/kg	Osmolar gap, mosM/kg
1	101	3.7	1.4	115	6.9	249	214	+35
2	108	4.5	1.7	270	6.5	252	229	+23
3	118	3.7	3.7	349	12.2	273	256	+17
4	128	3.6	5.5	442	10.0	284	275	+9