Hyponatraemia Syndrome in Acute Myeloid Leukaemia

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British Medical Journal, 1974, 1, 52-55

Summary

Hyponatraemia was observed in 11 out of 14 consecutive patients with acute myeloid leukaemia and its variants. Metabolic studies on these patients revealed an early increase in the urinary sodium excretion, negative free water clearance, and urine osmolality inappropriately higher than that of the serum. It is postulated that this syndrome is caused by a substance released from the primitive cells of the abnormal myeloid series.

Introduction

A state of low serum sodium had been seen to occur frequently during the course of their illness in patients with acute myeloid leukaemia and its variants. This paper presents pertinent data on 14 patients together with balance studies on two of these in whom hyponatraemia developed as the result of unexplained sodium wasting from the kidney.

Patients and Methods

To investigate the electrolyte disturbances often seen in association with acute leukaemia, Na and K balance studies were conducted on all newly-admitted patients with acute myeloid leukaemia. These studies were generally limited to a five-day period covering each admission and readmission to hospital. This study concerns 14 consecutive patients who were investigated in this manner. Two of these (cases 2 and 4, see below) were investigated intensively throughout the period of their stay in hospital. The effects of saline and fluid loads were studied in these two patients (figs. 1 and 2). The values of dietary Na, K, and nitrogen were calculated by the method of McCance and Widdowson (1969). Food eaten was accounted for in the final analysis of these values.

Twenty-four-hour urine collections beginning at 8 a.m. each day were made, using chloroform as preservative. Blood samples were obtained and analysed on the same day. Body weight was measured after voiding. The measurements of Na and K were carried out with a flame photometer and those of urea and chloride in a Technicon AutoAnalyzer. Osmolality of serum and urine was determined by advanced osmometer. However, in case 4 on days 1, 2, 5, and 12 (fig. 2) osmolality of urine was estimated indirectly—that is $2(\text{Na} + \text{K}) +$

Urea mg/l.

Mol. Wt. of urea (= 60)

Plasma cortisol was determined fluorometrically (Mattingly *et al.*, 1964) and serum thyroxine by the T-4 column test (Biorad Co.). Plasma arginine vasopressin was determined by radioimmunoassay (Beardwell, 1971). Other investigations were performed by standard laboratory methods.

Case Reports

Case 2.—A 58-year-old woman was admitted to hospital from the casualty department which she had been attending for treatment of an ulcer on her right thigh. A routine blood count had shown a haemoglobin level of 9.1 g/100 ml, platelets 91,000/mm³, and a white cell count of 2,800/mm³ with 15% blast cells. On examination she was febrile and found to have moderate hepatosplenomegaly. A bone marrow aspiration showed a highly cellular specimen with myeloblasts accounting for 95% of the cells. Initial laboratory investigations showed blood urea, serum electrolytes, plasma proteins, hepatic function tests, immunoglobulins, and urine analysis to be within normal limits. A diagnosis of acute myeloid leukaemia was made and the patient was admitted to the sixth M.R.C. trial. On the third day in hospital induction therapy, consisting of a single intravenous administration of daunorubicin (1.5 mg/kg body weight) and five daily intravenous injections of cytosine arabinoside (2 mg/kg/day), was begun. She was also given a combination of ampicillin and cloxacillin 250 mg of each drug six-hourly by mouth. Serum electrolytes were estimated daily. On the 12th day in hospital a second course of daunorubicin and cytosine arabinoside was started. Four days later serum electrolytes and blood urea showed the following values: Na 128 mEq/l., K 4.6 mEq/l., Cl 98 mEq/l., blood urea, 25 mg/100 ml. Plasma cortisol and serum T-4 column iodine were within normal limits. The hyponatraemia was associated with the formation of a hypertonic urine (fig. 1). She remained pyrexial. The administration of ampicillin and cloxacillin was discontinued and a combination of gentamicin (60 mg) and carbenicillin (1 g) was given six-hourly by intravenous infusion. The patient complained of a headache and nausea on two occasions during the period of hyponatraemia. The blood urea dropped to 6 mg/100 ml. Towards the end of the study her fluid intake was restricted and serum Na rose to 138 mEq/l. (fig. 1).

Case 4.—This 44-year-old man had had frequent night sweats for nine weeks. He was a known diabetic taking chlorpropamide 250 mg daily. His doctor suspected acute leukaemia and initiated corticosteroid therapy (prednisolone 50 mg/day). On admission to hospital he was pale and febrile. Initial investigations showed

FIG. 1—Case 2. Fluid and sodium balance study

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TABLE I—Haematological Data and Serum Sodium Values in 14 Patients with Acute Leukaemia

Case No.	Days after Diagnosis	Blast Cell Count		Serum Na (mEq/L)	Diagnosis (Acute Leukaemia)	Cytotoxic Therapy (No. of Courses*)	Other Treatment
		Bone Marrow (%)	Peripheral Blood Absolute ($\times 10^9$)				
1	2	90	0.28	140	Myeloblastic	None	Gentamicin, cephaloridine
	36	5	0.07	126		3	
2	6	95	0.42	141	Myeloblastic	None	See case report
	21	40	0.05	128		2nd course	
3	4	70	5.40	141	Myeloblastic	None	Gentamicin, cephaloridine, carbenicillin
	55	10	0.96	137		4	See case report
4	1	90	141.81	132	Myelomonocytic	None	Gentamicin, cephaloridine
	4	75	120.54	129		None	See case report
5	2	90	14.20	139	Myelomonocytic	None	Gentamicin, cephaloridine
	15	30	None	133		1	
6	5	70	0.88	139	Myeloblastic	None	Prednisolone 60 mg/day
	56	15	0.02	126		3	
7	1	80	0.40	137	Myeloblastic	None	Ampicillin, gentamicin, carbenicillin
	19	20	None	127		2	
8	7	80	34.20	140	Myeloblastic	None	Gentamicin, cephaloridine
	11	?	3.00	133		1	
9	6	59	5.10	136	Myeloblastic	None	Gentamicin, cephaloridine
	13	45	0.05	134		1	
10	2	72	45.50	135	Myeloblastic	None	Cephaloridine, carbenicillin
	4	?	67.60	132		None	
11	10	80	0.19	141	Myeloblastic	None	Prednisolone 120 mg/day
	17	10	None	137		1	
12	2	90	45.60	133	Myeloblastic	None	Gentamicin, cephaloridine
	13	50	None	134		1	
13	4	90	23.80	138	Myelomonocytic	None	Thyroxine 0.1 mg/day
	26	30	12.60	133		1	
14	5	90	0.40	144	Myeloblastic	None	None
	42	15	0.48	136		3	

* One course = A single intravenous administration of daunorubicin and five daily injections of cytosine arabinoside.

normal values for plasma proteins, serum iron, immunoglobulins, and for hepatic function studies. Routine urine analysis showed glycosuria, and the blood sugar was 120 mg/100 ml. The haemoglobin was 9.1 g/100 ml, platelets 50,000/mm³ and W.B.C. 163,000/mm³ (87% myeloblasts and monocytoid blast cells). The serum Na was 132 mEq/L, serum K 3.5 mEq/L, C1 90 mEq/L, and blood urea was 42 mg/100 ml. The diagnosis of acute myelomonocytic leukaemia was confirmed by a bone marrow examination. It was decided to tail off prednisolone and begin antibiotic and cytotoxic therapy. Gentamicin (80 mg eight-hourly) and cephaloridine (500 mg six-hourly) were administered by intravenous infusion. The serum Na level fell to 129 mEq/L before starting the cytotoxic therapy. There was no clinical or laboratory evidence of adrenal, thyroid, hepatic, or renal insufficiency. A five-day induction course of cytotoxic therapy was initiated. Prednisolone and chlorpropamide were discontinued and the diabetic state was adequately controlled with soluble insulin 20 units twice a day.

FIG. 2—Case 4. Fluid and sodium balance study. Note negative free water clearance (tubular clearance of water) throughout period of study.

The hyponatraemia continued throughout the period of the study (fig. 2) despite the withdrawal of chlorpropamide. The blood urea dropped to 12 mg/100 ml. He was discharged 17 days after admission. He was readmitted on two more occasions and found to have a low serum Na concentration which returned to normal on each occasion when his oral intake of fluids was restricted to less than 2 l./day.

Results

Hyponatraemia (serum Na <135 mEq/L) developed in 11 of the 14 patients (78%). Three of these 11 patients (cases 4, 10, and 12) had a low serum Na level on admission before any cytotoxic therapy had been initiated (table I). One (case 4) was taking chlorpropamide and prednisolone (see Case Report) but the other two patients had not received drugs before the development of hyponatraemia. Two other patients (cases 7 and 9) had serum Na levels in the lower range of normal (table I) before any treatment had been started, and these levels dropped further after induction therapy. Four of these five patients had a high absolute blast cell count. The remaining six patients developed hyponatraemia after antileukaemic therapy. In each of these six cases a considerable fall in the blast cell count (bone marrow and peripheral blood) coincided with a fall in the serum Na level (table I). Some reduction in the serum Na level was

TABLE II—Sodium Balance, Urinary, and Serum Osmolality Values in 14 Patients with Acute Leukaemia

Case No.	Osmolality* (mOsm/kg)		Na Intake (mEq/day)	Urinary Na (mEq/day)	
	Serum	Urine		Before Therapy†	During Therapy†
1	264	680	65-75	56	22-99
2	255	460	52-100	65	55-280
3	274	412	65-78	?	92-150
4	260	416	120-256	204	157-485
5	286	384	145-230	5	95-133
6	268	647	72-140	186	126-324
7	258	429	74-140	20	45-138
8	254	422	70-140	?	124-319
9	274	490	68-220	2	91-176
10	284	364	220-405	18-94	194-495
11	276	432	60-95	295	72-221
12	272	540	65-130	19	59-153
13	270	421	65-110	84	123-301
14	276	?	68-75	?	105-136

*At onset of hyponatraemia.

†Cytosine arabinoside and daunorubicin.

seen to occur in association with a fall in the blast cell count in all patients who received cytotoxic therapy.

Sodium Balance Studies.—Patients were allowed a sodium intake of 60–85 mEq/day. Variations in either direction occurred as a result of poor appetite and intravenous therapy. Pretreatment urine collection was incomplete in three patients but urinary Na values were obtained in the other 11 before induction therapy (table II). Seven of these patients were in positive Na balance but their urinary sodium excretion increased appreciably during induction therapy. The pretreatment urinary excretion of Na was high in three patients and this remained raised during antileukaemic therapy (table II). It is noteworthy that these three patients with a significant natriuresis were on high doses of prednisolone (table I). An increase in salt intake led to a further loss of Na in urine in all the 14 patients (table II) without any significant improvement in the serum Na level (see figs. 1 and 2).

Urine and Serum Osmolality.—The urine was found to be consistently hypertonic to the serum at the onset of hyponatraemia in all the 11 patients (table II).

Effects of Variation in Fluid and Sodium Intake.—Two patients (cases 2 and 4) were investigated in some depth in order to study the effects of alteration of salt and fluid intake. Both were febrile throughout the period of the study and were allowed free access to fluids. One (case 4) drank copiously and his intake, including intravenous fluids, ranged between 4 and 6 l./day. A severe reduction to below 2 l./day corrected hyponatraemia on two occasions. The other patient maintained a fluid intake of from 2 to 3 l./day. Her water intake was reduced to 800 ml/24 hr on the 19th day of the study. This led to a fall in the urinary output and the serum Na increased to 137 mEq/l. (fig. 1). The saline load was increased on days 6 to 9 in case 2. Diuresis ensued with a fall in the urine osmolality (fig. 1). The body weight increased by 2 kg. Sodium intake was increased on days 12 and 17. This aggravated the salt loss in the urine and the serum Na level fell to its lowest level of 118 mEq/l. on day 12. Similar results were obtained in case 4. The increased Na intake was promptly passed in the urine giving an overall negative Na balance (fig. 2). The first step in the chain of events in these two patients was an increase in the urinary Na excretion, and this increased further after an increased salt intake with only a transient improvement in the serum Na level. Both patients failed to excrete osmotically-free water and elaborated urine inappropriately hypertonic to the serum. A severe restriction in the fluid intake led to an increase in the serum Na level.

Other Studies.—The plasma arginine vasopressin level was found to range between 0.7 and 1.8 pg/ml in three patients (cases 1, 2, and 12) at the height of their hyponatraemia. These values are considered to be at the lower limit of the normal range. (C. G. Beardwell, personal communication, 1973). Plasma cortisol was determined at 10 a.m. on two consecutive days in 11 patients and the average of the two values is shown in table III. There was no adrenal or thyroid insufficiency as determined by plasma cortisol and T-4 column iodine levels (table III). One patient (case 13) was on L-thyroxine because of previously diagnosed hypothyroidism, but this appeared to be

well controlled with treatment and the patient showed no clinical or laboratory evidence of thyroid deficiency. Renal function as determined by creatinine clearance estimations, urine analysis, and blood urea levels was found to be adequate at the onset of hyponatraemia in all patients. Blood urea levels fell with the development of hyponatraemia in all patients and values below 15 mg/100 ml were observed in four patients (cases 1–4).

Discussion

The low serum Na state did not appear to be related to therapy in two patients (cases 10 and 12) who developed hyponatraemia before any treatment had been started (table I). One patient (case 4) had been on chlorpropamide and prednisolone before the development of hyponatraemia. Chlorpropamide therapy has been found to induce fluid retention and hyponatraemia but the syndrome abates after withdrawal of the drug (Fine and Shedrovitzky, 1970; Weissman *et al.*, 1971). Hyponatraemia persisted in case 4 despite the cessation of chlorpropamide therapy.

The patients reported on here presented a syndrome characterized by natriuresis, hyponatraemia, and failure to excrete osmotically-free water. These features resemble those associated with inappropriate secretion of antidiuretic hormone. This syndrome was first described by Schwartz *et al.* (1957) in two patients with bronchogenic carcinoma. Awareness of this association has brought to light a wide variety of conditions in which an abnormally sustained secretion of antidiuretic hormone has been invoked to explain hyponatraemia (Bartter and Schwartz, 1967). Though reported to occur in Hodgkin's disease (Spittle, 1966), so far as we are aware acute leukaemia has not been known to be associated with this syndrome.

It appears unlikely that the low serum Na state in these patients was due to an excess of antidiuretic hormone since plasma arginine vasopressin levels were found to be normal in three patients with the syndrome. The data available here favour the conclusion that this syndrome of hyponatraemia was induced by a natriuretic substance which was not antidiuretic hormone but resembled it in most of its actions. The most prominent feature in seven of the 11 patients was an increase of natriuresis after the administration of cytotoxic therapy with a consequent fall in the serum Na level (tables I and II). The three patients excreting large quantities of Na before induction therapy were taking high doses of prednisolone. It was a paradoxical phenomenon since corticosteroids are well known for their salt-retaining effect (Lange and Doorenbos, 1972). Occasionally *hypernatraemia* has been observed to develop after the administration of pharmacological doses of corticosteroids (Sawyer *et al.*, 1967). It is possible that this phenomenon of natriuresis associated with the administration of prednisolone in these three patients may have had the same basis as the augmented natriuresis induced by cytotoxic therapy in the other seven patients. Corticosteroids have non-specific antileukaemic properties and have been reported to induce remission in a significant proportion of patients with acute leukaemia (Fessas *et al.*, 1954; Sampey, 1963). It would seem reasonable to postulate that this syndrome of hyponatraemia may be caused by a natriuretic substance released from leukaemic cells. This substance may have been released as a result of wear and tear during a high turnover of blast cells in four patients with a high absolute blast cell count who had hyponatraemia before antileukaemic therapy.

The concept that primitive cells of the myeloid series secrete a natriuretic substance is not an exaggeration of the functional scope of these cells. Leucocytes are thought to produce a significant portion of vitamin B₁₂-binding alphaglobulin (Simons and Weber, 1966), and there is enough evidence to indicate that white blood cells are a source of a low molecular weight protein, lysozyme (Barnes, 1940; Osserman and Lawlor, 1966). However, the conclusion that an antidiuretic-hormone-like substance is released from the white cells is speculative, and further studies are required to prove it.

The presence of this syndrome in a high proportion of patients

TABLE III—Creatinine Clearance, Plasma Cortisol, and Serum T-4 Column Iodine Levels in 11 Patients with Hyponatraemia

Case No.	T-4 Column Iodine (ug/100 ml)	Plasma Cortisol (ug/100 ml)	Creatinine Clearance (ml/min)
1	3.3	23	85
2	3.3	20.5	100
4	4.2	15	110
5	3.6	14	111
6	4.7	11.5	85
7	3.6	13.5	100
8	4.5	12.6	77
9	4.6	16.5	132
10	5.9	18	83
12	4.1	11.5	116
13	6.1	19	162
Normal range (6 subjects)	2.3–6.1	10–30	75–130

with acute myeloid leukaemia is of great clinical importance. Water intoxication may produce confusion (Kaye, 1966) and disorientation (Weissman *et al.*, 1971)—symptoms which can readily be confused with the terminal state of acute leukaemia. Intravenous infusion can be hazardous in these patients. Attention to the underlying electrolyte imbalance will lead to the correct diagnosis, which is reversible by water restriction.

We appreciate the kind co-operation of Dr. C. G. Beardwell, of the Clinical Research Laboratories, Christie Hospital, and Holt Radium Institute, Withington, Manchester, in performing radio-immunoassay for the determination of plasma arginine vasopressin. Our thanks are due to Dr. J. D. Swales for his helpful criticism.

References

Barnes, J. M. (1940). *British Journal of Experimental Pathology*, **21**, 264.

Bartter, F. C., and Schwartz, W. B. (1967). *American Journal of Medicine*, **42**, 790.
 Beardwell, C. G. (1971). *Journal of Clinical Endocrinology*, **33**, 254.
 Fessas, P., Wintrobe, M. M., Thompson, R. B., and Cartwright, G. E. (1954). *Archives of Internal Medicine*, **94**, 384.
 Fine, D., and Shedrovitzky, H. (1970). *Annals of Internal Medicine*, **72**, 83.
 Kaye, M. (1966). *American Journal of Medicine*, **41**, 910.
 Lange, W. E. de, and Doorenbos, H. (1972). In *Side Effects of Drugs*, ed. L. Meyler, vol. VII, p. 525. Amsterdam, Excerpta Medica.
 McCance, R. A., and Widdowson, E. M. (1969). *The Composition of Foods*, 3rd edn. London, H.M.S.O.
 Mattingly, D., Dennis, P. M., Pearson, J., and Cope, C. L. (1964). *Lancet*, **2**, 1046.
 Osserman, E. F., and Lawlor, D. P. (1966). *Journal of Experimental Medicine*, **124**, 921.
 Sampey, J. R. (1963). *American Journal of Pharmacy*, **135**, 380.
 Sawyer, R. B., Spencer, J. R., Dudzenski, P. J., and Enis, J. E. (1967). *American Journal of Surgery*, **114**, 691.
 Schwartz, W. B., Bennett, W., Corelop, S., and Bartter, F. C. (1957). *American Journal of Medicine*, **23**, 529.
 Simons, K., and Weber, T. (1966). *Biophysics Acta*, **117**, 201.
 Spittle, M. F. (1966). *Postgraduate Medical Journal*, **42**, 523.
 Weissman, P. N., Shinkman, L., and Gregerman, R. I. (1971). *New England Journal of Medicine*, **284**, 65.

Remission of Diabetes Mellitus during Pregnancy

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British Medical Journal, 1974, **1**, 55-57

Summary

Two cases are reported in which a remission of diabetes was sustained throughout pregnancy. This seemed to be due in part to improved β -cell function consequent on restoration of normoglycaemia before pregnancy, and in part to an increase in insulin sensitivity during pregnancy, which in the first case disappeared very rapidly after delivery.

Introduction

Though partial remission of diabetes is not uncommon in young diabetics soon after control has been established the return to normal glucose tolerance is rare (Harwood, 1957; Peck *et al.*, 1958; Stutman and Hayes, 1959; Hines and Kessler, 1961; Field *et al.*, 1961; Brereton, 1968). For glucose tolerance to remain normal throughout pregnancy in a diabetic is even more remarkable. It seemed of interest, therefore, to report two cases in which remission of diabetes persisted during pregnancy, the response to 50-g oral glucose tolerance tests remaining normal throughout in one and nearly normal in the other.

Case 1

This patient was found to be a diabetic at the age of 29 when she presented with a three-month history of recurrent boils. There were no other symptoms and she was of normal weight. The blood glucose in the mid-morning at her first clinic visit was 302 mg/100 ml (G.O.D. period method, Boehringer). After one month on a 150-g carbohydrate diet her mid-morning blood glucose was 334 mg/100 ml. She was therefore given chlorpropamide 250 mg daily (fig. 1). After starting chlorpropamide, and until after delivery, all mid-morning blood glucose values were below 120 mg/100 ml (mean

FIG. 1—Case 1. Mid-morning blood glucose values over two-year period. Readings taken two to three hours after a meal.

83 mg/100 ml). All urine tests done twice daily throughout pregnancy were negative for sugar. Chlorpropamide was discontinued at 32 weeks of pregnancy. Between the 33rd and 37th weeks four 50-g oral glucose tolerance tests were done (table I). The highest one-hour value was 173 mg/100 ml and the highest two-hour value 123 mg/100 ml. (A 100-g oral glucose tolerance test at 35 weeks, however, produced a two-hour blood glucose of 175 mg/100 ml, and response to a cortisone glucose tolerance test (Fajans and Conn, 1961) was grossly abnormal at 38 weeks). Serum insulin (Hales and Randle, 1963) was low throughout all these tests for this stage of pregnancy. Plasma placental lactogen (Letchworth *et al.*, 1971) estimated during each test was within the normal range (table I). Twenty-four-hour urinary oestriol (Brombacher *et al.*, 1968) measured on 11 occasions from the 32nd week was also normal, ranging from 10.5 to 44.3 mg/24 hours.

Glycosuria reappeared four days after delivery and glucose tolerance deteriorated rapidly thereafter (fig. 2).

The baby, delivered at 38 weeks, was a typical infant of a diabetic mother, weighing 4,360 g at birth. The placenta was also a little heavy (51 g). The baby rapidly became hypoglycaemic, cord blood glucose dropping from 88 mg/100 ml at birth to less than 10 mg/100 ml one hour later, when an intravenous glucose infusion was started. In spite of a continuous glucose infusion and glucagon

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