Osmolar relation between cerebrospinal fluid and serum in hyperosmolar hypernatraemic dehydration

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Habel, A. H., and Simpson, H. (1976). *Archives of Disease in Childhood*, **51**, 660. **Osmolar relation between cerebrospinal fluid and serum in hyperosmolar hypernatraemic dehydration.** The relation between cerebrospinal fluid (CSF) and serum osmolality was studied in 16 patients with hyperosmolar hypernatraemic dehydration before treatment. After correcting shock and acidosis, 0.45% saline in 2.5 or 5% dextrose was infused in each patient over a 48- to 72-hour period. During rehydration, serum osmolality, electrolyte concentrations, urea nitrogen, and blood pH were measured sequentially.

Five patients developed severe neurological abnormalities within 48 hours of admission (convulsions 2, convulsions with hemiplegia 2, hemiplegia 1). Of these, 3 had residual defects on follow-up at least one year later. This group was indistinguishable from the 11 without significant neurological abnormality, both on clinical grounds before rehydration, and after analysis of admission and subsequent serum biochemical variables.

A significant osmolar gap (>4 mmol/kg H_2O) between serum and CSF was found in 13 patients. Severe neurological disturbance only occurred when CSF osmolality exceeded that of serum by 7 or more mmol/kg H_2O . Discriminant analysis of the paired osmolar data showed that $D = -117 + 1.74 \times (\text{CSF osmolality}) - 1.41 \times (\text{serum osmolality})$, and that severe neurological abnormality was predicted when D was positive.

The mortality rate among children with hyperosmolar hypernatraemic dehydration (HHD) varies from 8 to 20%. Mental retardation, epilepsy, and cerebral palsy are the sequelae in 9-11% of survivors (Macaulay and Watson, 1967; Morris-Jones, Houston, and Evans, 1967). The main causes of death are cerebral vessel thrombosis, haemorrhagic encephalopathy (Elton, Elton, and Nazareno, 1963), and cerebral oedema (Morris-Jones *et al.*, 1967). The treatment of this condition is controversial. Rapid administration of dilute solutions may cause osmotic dysequilibrium between blood and brain tissue resulting in cerebral oedema. In this situation it has been shown experimentally (Arieff *et al.*, 1972) that the osmolality of cerebrospinal fluid (CSF) reflects that of brain tissue. A significant osmolar gap between CSF and blood has been shown in diabetic patients with hyperosmolar ketoacidosis (Ohman *et al.*, 1971). We measured

CSF and serum osmolality before rehydration in children with HHD and related our findings to the occurrence of immediate and long-term neurological complications. Using a standard regimen for rehydration we have assessed prospectively the predictive value of our initial osmolar findings and those based on serial determinations of serum osmolality, electrolytes, urea nitrogen, and acid-base variables during the course of rehydration.

Patients

Twenty-eight children were admitted to the Royal Hospital for Sick Children, Edinburgh, between March 1972 and March 1974 with HHD, defined as serum $Na \geq 150$ mmol/l or a serum osmolality >310 mmol/kg water on admission. 16 were selected for study, the sole additional criterion being the need to obtain lumbar CSF to exclude meningitis. The previous health and neurological development of these children was normal, except for one child with multiple congenital abnormalities and mild mental retardation.

Received 11 December 1975.

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A further 12 children aged 6 months to 11 years, investigated for suspected meningitis, provided 'control' samples of CSF and serum taken simultaneously. Cell counts, glucose, and protein concentrations were within normal limits and bacterial and viral cultures were negative in the CSF samples obtained from these patients.

Methods

The clinical condition of each patient was assessed on admission to hospital (Table I). Clinical reappraisal was made 6- to 8-hourly by one of us (A.H.) during the course of rehydration for at least 48 hours, giving particular attention to neurological status. Throughout that period constant nursing care was maintained. Following apparent recovery the clinical status of each child was reviewed periodically for at least one year. Psychological assessments were performed when age permitted (Cases 1, 14 in Table I) using the Stanford Binet Form L-M, the Goodenough Draw-a-man test, and the Vinceland Scale of Social Maturity.

Initial blood specimens were obtained before treatment for measurement of osmolality and the concentrations of sodium, potassium, calcium, chloride, urea nitrogen, and glucose. pH , PCO_2 and base excess were determined in arterial or arterialized capillary blood. Serum osmolality, electrolytes, and urea nitrogen were measured serially thereafter 8- to 12-hourly until rehydration was completed. Capillary blood glucose concentration was monitored 4- to 6-hourly using Dextrostix (Ames).

In 10 patients CSF and initial venous blood samples were obtained simultaneously. Lumbar puncture was delayed unavoidably up to one hour in the remaining 6 (Cases 1, 5, 8, 12, 14, 15) because of the more urgent need for resuscitation. Osmolality, Na and K concentrations were measured in these samples (Table II), in addition to the routine biochemical and bacteriological investigations.

The protocol for rehydration, similar to that recommended by Finberg (1973) and Winter (1968), comprised three phases. (1) In the presence of shock circulating blood volume was re-expanded with full-strength plasma or 5% albumin, 10-20 ml/kg intravenously over 30 minutes. (2) If pH was <7.25 half the total correction was undertaken with 8.4% $NaHCO_3$ infused over 20 minutes. (3) Fluid replacement, orally or intravenously, was maintained at a constant rate over 48-72 hours, initially as 0.45% saline in 2.5% or 5% glucose water. The volume given was the sum of (i) the estimated fluid deficit, (ii) no more than 80% (Winter, 1968) of normal fluid requirements (Holliday and Segar, 1957), and (iii) estimated ongoing losses. The cation concentration of the repair solution was maintained between 70 and 80 mmol/l adjusting the Na content when K or Ca was added. Na salts of antibiotics, administered in every case, contributed 0.5-2 mmol/day. Each patient was weighed twice daily.

Additional supportive therapy included the administration of oxygen when shock was present. Dexamethasone and mannitol were given to one patient (Case 2) in whom signs of raised intracranial pressure were attributed to cerebral oedema. Mechanical ventilation was maintained for 50 hours in Case 13.

Laboratory methods. An advanced Instruments Osmometer* (Model 3W) measured osmolality in 0.2 ml samples of serum and CSF. Eight successive measurements of a 300 mmol/kg water standard showed 1 SD about the mean of 0.5 mmol/kg water. Linearity over the range 100-500 mmol/kg water was shown using freshly prepared reference solutions of NaCl. The instrument was calibrated before and after each batch of measurements. Duplicate measurements agreed to

*Advanced Instruments Inc., 1000 Highland Avenue, Needham Heights, Mass. 02194.

TABLE I
Clinical details on admission

Case no.	Sex	Age (m)	Diagnosis	Predominant symptoms	Duration (d)	Dehydration* (%)	Shock†	Activity in preceding 24 hours
1	F	36	GE	Diarrhoea	3	7.3	+	Apathetic
2	M	16	GE	Diarrhoea + vomiting	7	9.1	-	Jittery
3	M	1.5	UTI	Diarrhoea + vomiting	2	12.8	+	Apathetic
4	F	3	UTI	Polyuria	1	13.5	+	Jittery
5	M	8	GE	Diarrhoea + vomiting	3	12.5	+	Convulsions, 2 h
6	M	6	GE	Diarrhoea + vomiting	2	6.9	-	Irritable
7	M	24	GE	Diarrhoea + vomiting	5	7.6	-	Jittery
8	F	5	GE	Diarrhoea + vomiting	4	9.1	+	Irritable
9	M	0.5	UTI	Polyuria	7	15.4	+	Apathetic
10	M	3	Pneumonia	Vomiting	4	5.0	-	Irritable
11	M	2	GE	Vomiting	7	6.7	-	Apathetic
12	M	8	GE	Hyperventilation	6	12.3	+	Irritable
13‡	M	3	GE	Diarrhoea + vomiting	5	12.8	+	Apathetic
14	M	24	GE	Diarrhoea + vomiting	3	12.5	+	Apathetic
15	M	0.5	GE	Diarrhoea + vomiting	6	14.2	+	Irritable
16	M	1.5	GE	Diarrhoea + vomiting	1	8.0	+	Irritable

*Calculated from admission weight and final steady weight.

†Defined clinically as pallor, tachycardia, and barely palpable peripheral pulses. ‡Cardiorespiratory arrest.

GE, Gastroenteritis; UTI, urinary tract infection.

TABLE
Serum and CSF osmolalities

Case no.	Serum				
	Osmolality (mmol/kg H ₂ O)	Na ⁺ mmol/l	K ⁺ mmol	Cl ⁻ mmol/l	Urea nitrogen mmol/l (mg/100 ml)
1	321	148	2.6	124	28.3 (79)
2	357	155	4.8	119	57.8 (162)
3	390	163	6.1	139	48.2 (135)
4	357	158	5.8	136	59.2 (166)
5	367	165	5.3	127	17.9 (50)
6	330	156	5.0	120	17.9 (50)
7	324	150	4.6	113	13.9 (39)
8	389	185	5.8	136	32.5 (91)
9	363	154	7.9	124	52.5 (147)
10	347	162	5.6	131	12.8 (36)
11	340	154	5.1	131	14.3 (40)
12	405	169	7.0	129	41.0 (115)
13	340	153	8.8	120	15.0 (42)
14	380	160	4.3	117	24.3 (68)
15	393	158	6.1	134	41.1 (117)
16	337	156	5.6	141	29.3 (82)

within 2 mmol/kg, the final result being expressed as the mean of 2 or 3 determinations in each specimen. The remaining biochemical and acid-base measurements were made by routine laboratory methods.

Results

All 28 patients survived. During the first 72 hours severe neurological abnormalities developed in 5 cases—convulsions (Cases 1, 3), convulsions and hemiplegia (Cases 2, 5), and hemiplegia alone (Case 4). Table III shows the timing and duration of these abnormalities.

Of the remaining patients, all but one (Case 13) showed only minor neurological abnormalities during treatment—apathy (Cases 7, 8, 12, 14), jitteriness (Cases 9–11, 15, 16), and transient hypertonia (Cases 7, 12, 15, 16). One infant (Case 13) was resuscitated after a cardiorespiratory arrest before treatment. Recovery was complicated by focal seizures and hemiplegia, renal tubular necrosis, and disseminated intravascular coagulation. No neurological abnormalities were detected, however, at follow-up 13 months later. Cerebral hypoxia was considered to be the primary cause of his neurological disturbance

TABLE III
Clinical progress of neurologically abnormal patients

Case no.	Age (m)	Sex	Neurological abnormality	Onset and duration	EEG changes	Follow-up	Duration of follow-up (m)
1	36	F	Unrousable, limb myoclonus	0 to 36 h	Normal at 3 d	Borderline IQ (82)*	24
2	16	M	Left hemiplegia; focal seizures	At 30 h for 72 h	Slight asymmetry at 1 m	Mild left hemiplegia	15
3	1.5	M	Grand mal	At 5 h for 5 min	Normal at 5 m	Motor development retarded by 9 m at 16 m	14
4	3	F	Left hemiplegia	At 12 h for 6 m	Normal at 3 d	Flexion spasms from 8 to 9 m of age; normal development at 13 m	12
5	8	M	Left-sided seizures	At 4 h for 5 min	At 3 days: 1 Hz spike-wave diffuse cortical abnormality; at 3 months: slight asymmetry	Motor development retarded by 6 m at 1 yr, normal at 18 m	13
			Left sided seizures with hemiplegia	At 53 h for 42 h			

*See methods.

II
and biochemistry on admission

Blood pH	Cerebrospinal fluid			CSF-serum difference	
	Osmolality (mmol/kg H ₂ O)	Na ⁺ mmol/l	K ⁺ mmol/l	Osmolality (mmol/kg H ₂ O)	Na ⁺ mmol/l
7.13	367	168	3.1	+46	+20
7.37	390	170	-	+33	+15
7.11	407	-	-	+17	-
7.33	370	165	-	+13	+7
7.18	375	157	-	+8	-8
7.37	337	168	-	+7	+12
7.38	326	161	3.2	+2	+11
7.06	390	170	3.4	+3	-15
7.12	361	153	3.5	-2	-1
7.38	338	-	3.4	+9	-
7.15	327	154	3.4	-13	0
7.14	388	174	3.6	-17	+5
7.28	323	-	-	-17	-
7.18	357	-	-	-23	-
7.09	366	-	-	-33	-
7.00	296	154	-	-41	-2

and he is excluded from the group in which major neurological manifestations may have resulted from, or been potentiated by, biochemical changes during rehydration.

The only neurological sequelae observed at follow-up 12-24 months later were in 3 patients (Cases 1, 2, 3, Table III) who showed severe neurological abnormalities during rehydration. One other patient with preceding mental retardation (Case 14) continued to achieve expected developmental milestones. Finally, analysis of our initial clinical findings on admission to hospital (Table I) showed that neurological sequelae could not have been predicted on that basis.

Osmolar relations. Of 12 control patients, mean CSF osmolality was 285 ± 11 (range 273-304) mmol/kg water, and mean serum osmolality 283 ± 11 (271-300) mmol/kg water. The mean difference between paired specimens of CSF and serum was 1.8 (SD 0.6) mmol/kg water. Under conditions of clinically normal hydration and serum Na within the normal range a difference of 4 mmol/kg water or more is significant.

Fig. 1. shows a direct relation between serum and CSF osmolality in the 16 patients with HHD. The difference between CSF and serum osmolality exceeded 4 mmol/kg water in 13 patients. The difference varied from 46 mmol/kg greater in CSF than serum (Case 1) to 41 mmol/kg greater in serum than CSF (Case 16). Severe neurological abnormalities were present when CSF osmolality exceeded that of serum by 7 or more mmol/kg. Fig. 1 also shows the result of discriminant analysis (Fisher's method) of this data. $D = -117 + 1.74 \times (\text{CSF}$

osmolality) $- 1.41 \times (\text{serum osmolality})$. Severe neurological disturbance was present only when D was positive. Persistent neurological handicap was found in those patients with the highest positive value for D (Cases 1, 2, 3). Analysis of paired values of Na (11 cases) and K (7 cases) in CSF and serum did not discriminate between patients with severe or minor neurological manifestations. CSF protein (mean 58 mg/100 ml, range 35-90 mg/100 ml) in patients with severe neurological abnor-

FIG. 1. Osmolar relation between CSF and serum. Under iso-osmolar conditions (controls) the line of correlation is shown ($x = 3.164 + 0.993 y$, $r = 0.989$). In HHD the line of discrimination between neurologically abnormal and normal patients is shown ($D = -117 + 1.74 \text{ CSF} - 1.41 \text{ serum}$).

malities did not differ significantly from CSF protein (mean 118, range 15–340 mg/100 ml) in the remaining cases.

Serum biochemistry. Serum osmolality, Na, urea nitrogen, and pH measured on admission were not significantly different in either group. The trends in these variables during rehydration were comparable in both neurologically normal and abnormal patients (Figs. 2–5). Hypocalcaemia and

FIG. 2.—Changes in serum osmolality during rehydration. (Δ Osm = value—first value below 305 mmol/kg H_2O). Initial rise in Case 1 was related to severe ongoing losses.

FIG. 3.—Changes in serum sodium during rehydration. (ΔNa^+ = value—first value below 148 mmol/l.) Initial rise in Case 1.

FIG. 4.—Changes in serum urea nitrogen during rehydration. (Δ serum urea nitrogen = value—first value below 9 mmol/l (26 mg/100 ml).) Normal levels were attained within 48 hours in 13 cases.

FIG. 5.—Changes in arterial/arterialized capillary pH during rehydration.

hypokalaemia were noted during rehydration in 4 patients (Cases 3, 4, 9, 14) but were not related by time of occurrence to neurological disturbance. Blood glucose concentration remained above 45 mg/100 ml (2.5 mmol/l) in all but one patient (Case 13) who developed transient hypoglycaemia.

Discussion

Using a conventional regimen of rehydration (Finberg, 1973) 5 of our 28 patients developed

major neurological complications, and in 3 there was evidence of chronic brain damage at follow-up 1 to 2 years later. By contrast, minor neurological dysfunction during rehydration was a transient phenomenon and all patients showing such signs had achieved normal developmental and neurological maturation at follow-up. The plan of treatment and subsequent follow-up assessment in the present series is broadly comparable with group A patients in the series of Bruck, Abal, and Aceto (1968), and the incidence of long-term neurological abnormality is similar—19% and 15% respectively. In the latter series, however, patients developing chronic handicap did not show severe neurological manifestations either before or during the course of initial treatment.

Our results indicate that in HHD there is nearly always a significant osmolar gap between CSF and serum, and that the greatest potential hazard exists when the osmolality of CSF is significantly higher than that of serum. A significant difference in the opposite direction does not appear to have the same prognostic implication. The unavoidable delay in obtaining CSF, in 6 cases, did not appear to influence the direction of this osmolar gap. Discriminate analysis of our initial osmolar data indicates that severe neurological complications might have been predicted. It is likely that this formula, based necessarily on static observations, will prove to be a useful guide rather than a precise predictor of neurological complications.

Determination of lumbar CSF/serum Na relation failed to identify neurologically abnormal cases. This could have been predicted from the outset, as half-time for equilibration of Na between ventricular and lumbar CSF is over 7 hours (Sweet *et al.*, 1954) compared with 5–50 minutes for water (Bering, 1952).

Arieff and his colleagues (1973) induced a hyperosmolar dehydration in rabbits using glucose. During rehydration with hypotonic saline and insulin they produced an osmolar gap of 39 mmol/kg across the blood/brain barrier, with a corresponding difference of 14 mmol/kg between CSF and serum. Severe cerebral oedema ensued, which supports a previous finding (Stern and Coxon, 1964) that a gap of 35 mmol/kg between brain and blood causes a shift of water into the brain.

Our findings do not support the view that in HHD osmotic equilibrium between brain and blood is restored rapidly by shifts of water. It seems likely that there are dynamic changes in osmotic gradients between the various body compartments during the development and treatment of HHD. Experimental confirmation is provided by Bering

and Avman (1960), who produced an osmolar gap between CSF and blood by rapid and slow (up to 75 minutes) intravenous infusion of urea in dogs. Initially water passed from the brain and CSF into blood. After 30 minutes the osmolar gradient reversed and the CSF osmolality exceeded that of serum. This persisted for some 5 hours and was associated with an increased intracranial pressure, presumably due to a transfer of water into the brain. Clinically this situation could arise from the administration of a large solute load or loss of water in excess of solute, and account for cyclical changes starting with raised serum osmolality above that of brain. The observed osmolar gap between CSF and serum in our patients is likely to be the resultant of different rates and directions of transfer of water, solutes, and possible osmotically active material of unknown aetiology, across the blood/brain and blood/CSF barriers (Arieff *et al.*, 1973; Finberg, Lutrell, and Redd, 1959; Stephenson, 1971). It is tempting to speculate that severe osmolar disequilibrium *per se*, perhaps exaggerated by therapy, was the mechanism of brain damage in our patients (Cases 1–5). On the other hand, the converse may be true and neurological or cerebrovascular damage might have caused the observed osmolar gradient. Intracranial haemorrhage favours a flux of water into the brain, reflected by the significant rise of CSF Na above that of plasma (Cooper, Lechner, and Bellet, 1955), as does acute cerebral hypoxia resulting from local capillary stasis and thrombosis (Battaglia *et al.*, 1958; Shaw, Alvord, and Berry, 1959; Adamsons and Myers, 1973). Blood was not present in the CSF in any of our patients, but 2 of the 3 with neurological residua were severely shocked. Whatever the mechanism(s) it seems important not to increase the osmolar gradient between CSF and blood in such cases during rehydration. It may be advantageous to reduce serum osmolality even more cautiously in the first few hours of rehydration by substituting 0.9% for 0.45% saline. This would allow more time for osmotic equilibrium between serum and brain and avoid further widening of the osmolar gap or excessive migration of water into already damaged cells. The hazards of excessive and prolonged administration of normal saline in hypo- and isonatremic dehydration are well known (Ahmed and Agosto-Odutola, 1970; Skinner and Moll, 1956), but we know of no reports of its use in HHD under controlled conditions other than in the initial emergency therapy. In the absence of a controlled clinical trial and follow-up assessment, firm recommendations on refinements of the therapeutic regimen employed are not possible.

We are grateful to Professor J. O. Forfar for support and encouragement; to Dr. N. Belton for providing biochemical facilities; to the staff of the Respiratory Laboratory and Department of Paediatric Biochemistry, Royal Hospital for Sick Children, Edinburgh, for unstintingly giving their time; to the paediatricians of the Royal Hospital for Sick Children, Edinburgh, who allowed us to study patients under their care; to Mr. J. C. Adams, of the Usher Institute of Community Medicine, for statistical help; to Mrs. J. Bechlofer, who carried out the psychological tests; and to Miss D. Housler, Mrs. P. Drake, and Miss S. Whitson for secretarial help.

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