ORIGINAL ARTICLE

Effect of salt supplementation of newborn premature infants on neurodevelopmental outcome at 10–13 years of age

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Background: The nutritional requirements of prematurely born infants are different from those of babies born at term. Inadequate or inappropriate dietary intake in the neonatal period may have long term adverse consequences on neurodevelopmental function. The late effect of neonatal sodium deficiency or repletion in the premature human infant on neurological development and function has not been examined, despite evidence in animals of a serious adverse effect of salt deprivation on growth of the central nervous system.

Methods: Thirty seven of 46 children who had been born prematurely (gestational age of 33 weeks or less) and allocated to diets containing 1–1.5 mmol sodium/day (unsupplemented) or 4–5 mmol sodium/day (supplemented) from the 4th to the 14th postnatal day were recalled at the age of 10–13 years. Detailed studies of neurodevelopmental performance were made, including motor function and assessment of intelligence (IQ), memory and learning, language and executive skills, and behaviour. Sixteen of the children were found to have been in the supplemented group and 21 in the unsupplemented group.

Results: Children who had been in the supplemented group performed better in all modalities tested than those from the unsupplemented group. The differences were statistically significant (analysis of variance) for motor function, performance IQ, the general memory index, and behaviour as assessed by the children's parents. The supplemented children outperformed the unsupplemented controls by 10% in all three components of the memory and learning tests (difference not significant but $p < 0.1$ for each) and in language function ($p < 0.05$ for object naming) and educational attainment ($p < 0.05$ for arithmetic age).

Conclusions: Infants born at or before 33 weeks gestation require a higher sodium intake in the first two weeks of postnatal life than those born at or near term, and failure to provide such an intake (4–5 mmol/day) may predispose to poor neurodevelopmental outcome in the second decade of life.

In earlier studies, we showed that preterm infants of less than 35 weeks gestation have obligate high renal[1] and intestinal[2] sodium losses during the first 2 weeks of life, leading to cumulative negative sodium balance in most and hyponatraemia in many. We further showed that increasing dietary sodium intake to 4 mmol/kg/day for infants born at 31–34 weeks, and to 5 mmol/kg/day for those born before 31 completed weeks, prevented the negative sodium balance and hyponatraemia and led to more rapid weight gain and earlier discharge from hospital.[3] The supplementary sodium (as the chloride salt) was given to 22 preterm infants from the 4th to the 14th day only, and a group of 24 unsupplemented babies served as controls. No adverse effects were seen. Similar results have been reported by others.[4 5]

It has been suggested that preterm infants are at risk of nutritional deficiencies that may impair growth and development if they are fed the same diet as term infants,[6–9] and that this may particularly affect the skeleton and nervous system.[10 11] In a recent study, hyponatraemia was found to be much more prevalent in very low birthweight babies who developed cerebral palsy than in comparable infants who did not (odds ratio 6.8, range 1.9–24.2)[12]; this odds ratio was higher than that for any other systemic or metabolic factor for which analysis was performed. In addition, there is a large body of experimental evidence that sodium deficiency is harmful to the growth and development of newborn animals.[13–20] We therefore decided to recall the 46 previously studied sodium supplemented and unsupplemented infants, to perform detailed assessments of their physical, neurological, psychological, and educational status at 10–13 years of age and to correlate their performance with their sodium intake in the neonatal period.

METHODS

Subjects

The hospital records of 43 of the 46 children in the earlier study[3] were located; 20 of these had received sodium supplements and 23 had not. Of these 43, one had died (sudden infant death syndrome), two had emigrated, two could not be found, and one refused to participate. Thus, 37 children were found and examined, of whom 16 had been supplemented and 21 had not. Table 1 gives the baseline characteristics of these two groups, and table 2 shows the plasma sodium concentrations before, during, and after the 10 day period of supplementation and the incidence of hyponatraemia. The infants in these studies were not prospectively randomised to control or supplemented groups, but belonged to two successive cohorts, the first of which were controls and the second supplemented. This was because the first (control) group was used to calculate the amount of sodium that would be predicted to prevent hyponatraemia and salt depletion; this amount was then given to the second (supplemented) group. The time between the two groups was a few weeks only, and no other aspect of management had changed in the interval.

The parents of each child were contacted and invited to participate in the follow up study. Each child was assessed by the same investigator (LJ), at home or at the hospital. The

Table 1 Comparison of the neonatal statistics of the unsupplemented infants (controls) and those supplemented with sodium

	Control (n=21)	Supplemented (n=16)
Non-white race	6	4
Female sex	8	9
Birth weight (g)	1473 (821–2100)	1538 (680–1980)
Gestational age (weeks)	30.2 (24.5–33)	31.3 (25–33)
Method of delivery		
SVD	16	10
LSCS	3	4
Breech	1	1
Forceps	1	1
Mean Apgar score		
5 minutes	6.5	6.3
10 minutes	8.4	8.4
Cranial ultrasound		
Normal	13	10
Abnormal	1	1
Not done	7	5
Ventilated	5	5
Type of feeding		
SMA	13	12
EBM + SMA	8	4

Where applicable, values are median (range). There were no significant differences between the groups.
SVD, Spontaneous vaginal delivery; LSCS, lower segment caesarian section; EBM, expressed breast milk.

children were tested on their own in two sessions lasting about 3.5 hours each without knowledge of whether the subject had been in the supplemented or control group. A school report was obtained for each child. Assessment included measurement of height, weight, and occipitofrontal head circumference using standard procedures.

Assessment of motor function

The Motor Assessment Battery for Children (MABC)[21] was used. This is a standardised test designed as a screening tool to identify children who fall within the lowest 15% of the population of age matched peers with respect to motor competence or functioning, and to identify and evaluate any movement disorder. The test contains eight items designed to assess aspects of manual dexterity, ball skills, and static and dynamic balance, and also yields an overall total score of motor functions.

Assessment of neuropsychological development

Intelligence was tested using the Wechsler Intelligence Scale for Children (WISC-III UK). This provides measures of verbal, performance, and full scale intelligence quotient (IQ). The average score in normal populations is 100 with a standard deviation of 15.

Memory and learning were assessed using the Wide Range Assessment of Memory and Learning (WRAML), which includes measures of verbal and non-verbal memory and learning presented in auditory and visual modalities.

Table 3 Comparison of age and standard morphometric measurements of infants in the control unsupplemented group and those supplemented with sodium at the time of study

	Control (n=21)	Supplemented (n=16)
Age (years)	11.8 (10.3–12.9)	11.9 (10.5–13.7)
Weight (kg)	42.5 (28.5–81.5)	40.7 (21.9–54.5)
Height (cm)	149.3 (137.5–162.7)	151.1 (134.0–169.0)
OFC (cm)	53.1 (49–56)	53.9 (49–57)
Mean height SDS	+0.47 (–1.9 to +12.03)	+0.25 (–1.77 to+2.94)

Data are presented as mean (range).
SDS, Standard deviation score; OFC, occipitofrontal head circumference.

Language functions were evaluated using the Wide Range Assessment Test (WRAT-2), the Children's Token Test, the British Picture Vocabulary Test (BPVT), and the Children's Graded Naming Test. These provide measures of both receptive and expressive language skills.

Executive functions were assessed by the Trail-Making Test, the Wechsler Mazes Test, the Word Fluency Test, and the Right-Left Discrimination Test.

Behaviour was assessed using the Rutter Behaviour Questionnaires which were completed by parents and teachers independently.

Statistical analysis

This was performed using analysis of variance, by the Mann-Whitney test, or by the χ^2 test (2×2 contingency table) as appropriate. $p < 0.05$ was chosen as significant.

RESULTS

Table 1 shows the characteristics of the two groups in the neonatal period. The mean gestational age of the infants in the supplemented group was slightly (1.1 weeks) but not significantly greater than that of the control infants. The plasma sodium concentrations were similar in the two groups before and during the period of supplementation, but significantly lower in the unsupplemented infants at 14–25 days (table 2); significantly more unsupplemented infants had at least one plasma sodium measurement < 130 mmol/l than did those in the supplemented group.

There were no differences between groups in age or standard morphometric measurements at the time of the present study (table 3).

The supplemented infants performed better than controls in all aspects of the MABC, the difference being significant for balance ($p = 0.0206$) and highly significant for manual dexterity ($p = 0.0029$) and the total score ($p = 0.0015$) (table 4). Similar differences were seen in the results of the WISC-3 Intelligence Scores (table 5). Children in the control group tended to be more likely ($p < 0.07$) than those in the supplemented group to show evidence of behavioural disturbance

Table 2 Plasma sodium concentration (mmol/l) and incidence of hyponatraemia (plasma sodium <130 mmol/l) in the unsupplemented and supplemented infants

	Control (n=24)	Supplemented (n=22)	p Value
Plasma sodium concentration:			
Before supplementation (day 2–3)	141.1 (5.1)	141.5 (4.3)	NS
During supplementation (day 5–11)	136.3 (7.1)	136.9 (4.6)	NS
After supplementation (day 14–25)	132.5 (5.3)	135.6 (3.4)	<0.025
Number of children with hyponatraemia	9 (37.5%)	4 (18.2%)	NS

Values are mean (SD).

Table 4 Results of the Motor Assessment Battery for Children (MABC) in unsupplemented control children and those supplemented with sodium

	Control (n=21)	Supplemented (n=16)	p Value
Manual dexterity	4.0 (0–14.5)	1.0 (0–8.0)	0.0029
Ball skills	0 (0–8.0)	0 (0–6.0)	NS
Balance	4.0 (0–12.0)	0 (0–8.0)	0.0206
Total score	11.0 (0.5–31.5)	2.25 (0–14.5)	0.0015
Percentile	1 (0.5–93)	74.5 (4–96)	0.0006

Data are presented as median (range). Lower scores indicate better performance in all parameters (except percentile).

Table 5 Results of the Wechsler Intelligence Scales for Children (WISC-3 UK)in unsupplemented control children and those supplemented with sodium

	Control (n=21)	Supplemented (n=16)	p Value
Verbal IQ	92.8 (65–130)	100.6 (57–136)	0.24
Performance IQ	86.9 (64–109)	100.5 (63–133)	0.03
Full scale IQ	88.8 (70–121)	100.4 (59–136)	0.08

Data are presented as median (range).

Table 6 Results of Rutter Questionnaires in unsupplemented control children and those supplemented with sodium

	Control	Supplemented	p Value
Parents' ratings	8/21	2/16	0.07
Teachers' ratings	5/19	1/8	NS

Values are numbers in each group showing evidence of behavioural deviance. p Value assessed by χ^2 test.

Table 7 Results of the Wide Range Assessment of Memory and Learning (WRAML) in unsupplemented control children and those supplemented with sodium

	Control (n=21)	Supplemented (n=16)	p Value
Verbal memory index	90.8 (62–122)	97.2 (57–121)	0.28
Visual memory index	90.0 (62–122)	96.8 (65–121)	0.19
Learning index	102.5 (62–122)	113.9 (89–145)	0.04
General memory index	94.5 (76–117)	103.4 (71–132)	0.10

Data are expressed as mean (range).

according to the parents' ratings (table 6); the same trend was seen in the teachers' ratings, although this did not reach statistical significance, perhaps because teachers' ratings were not obtained for all subjects. Supplemented children performed about 10% better than controls in each of the three components of the WRAML Test; the differences were significant for the learning index (p = 0.04; table 7). Similar differences were seen in each of the seven components of the WRAT-2 Test, although the differences only reached significance for object naming and arithmetic age (data not shown).

DISCUSSION

Several studies have found evidence of impaired motor function in infants born very prematurely,[22–26] with the degree of impairment in some of these, but not all, being inversely correlated with birth weight. Levene *et al*[27] investigating the relation between neonatal intracranial ultrasound scan findings and outcome at 5 years found impaired motor performance and lower Wechsler IQ scores in low birthweight infants compared with normal controls, even in the subgroup with consistently normal ultrasound appearances in the newborn period. The cause of this impaired performance is not clear, but there is both clinical and experimental evidence that nutritional factors may be of crucial importance for the early growth and development of the fetus and newborn, including that of the nervous system.

Gross[8] compared the effect of three diets on the early growth of premature infants. The diets consisted of pooled, mature human milk (M), milk expressed from the individual babies' own mothers (P), and a whey based formula (W); diets P and W contained more protein, Na^+, Cl^-, K^+, Ca^{2+}, and phosphorus than M. Growth was significantly greater with both the P and W diets than with M with respect to weight, crown-heel length, and head circumference. Although it is not possible to single out Na^+ as the sole or principal mediator of the differences, it was reported that hyponatraemia was significantly more common with the M diet (50%) than with P (15%) and W (20%). It is established that milk produced in the first few days of postnatal life by mothers who have given birth prematurely has a much higher sodium content than that produced by those who have given birth at term. Essentially identical results were obtained in several very similar studies published at about the same time.[6 7 9] In a later paper, Lucas *et al*[28] reported an impressive and significant difference in developmental status at 18 months of age in premature infants fed nutrient enriched preterm formula, similar in composition to the W diet in the previously cited paper by Gross,[8] or their own mothers' milk, compared with those fed standard term formula. The findings of Murphy *et al*[12] strongly suggest that neonatal hyponatraemia is an important risk factor for cerebral palsy in very low birthweight infants.

The adverse effect of sodium deprivation on somatic growth in fetal and newborn experimental animals has been shown in numerous studies[13 15–18 20 29] (for review see Haycock[30]). One study[14] specifically addressed the effect of four different dietary sodium intakes in the diet of pregnant rats on brain growth and development in their offspring. The diets provided sodium intakes ranging from 0.17 to 1.56 mmol/kg/day. The lowest intake group (0.17 mmol/kg/day) produced no offspring that survived the period of lactation (during which sodium was not restricted). In the remaining three groups, in those offspring that survived to weaning (21 days), maternal sodium intake correlated strongly with brain weight (wet and dry), cholesterol content, protein/DNA ratio, and RNA/DNA ratio, although differences in total birth weight had disappeared by this time. The last third of pregnancy in the rat corresponds roughly to the neonatal period in the human with regard to organ growth and differentiation.

The results of this study show that motor and neuropsychological development of a group of premature infants, studied at 10–13 years of age, was greatly influenced by whether or not they had received sodium supplementation of their feeds during the neonatal period (postnatal days 4–14). The 16 children in the supplemented group had significantly better developed motor skills (table 3) and perceptual organisation skills and superior IQs (table 4) than the 21 in the unsupplemented control group. The results are quite similar to those reported by Lucas *et al*[28 31] in 210 children who were fed on their own mothers' milk or nutrient enriched preterm formula milk as compared with 90 children fed standard term formula milk. The "enriched" group had significantly higher verbal, performance, and full-scale IQs than those fed on the standard formula, results very similar to those reported here (table 4). The finding in this and other studies[22–26] that motor skills seem to be particularly adversely affected may reflect the experimental observation that the cerebellum is the part of the brain most susceptible to early malnutrition.[32–35]

Birth is normally followed by a physiological contraction of the extracellular fluid amounting to a weight loss of about 5–15% in premature babies. Replacing sodium lost in the first few days is therefore contraindicated, because prevention of this fluid contraction is associated with adverse effects on cardiopulmonary function[36 37] and, possibly, an increased risk of chronic lung disease of prematurity.[38] Delaying the onset of sodium supplementation until 4–5 days of age[3 5] or until a measured weight loss of 6% has occurred[39] avoids these hazards while preventing the early and late adverse effects of cumulative sodium deficiency over the first 2–3 weeks.

In conclusion, we consider that the most likely explanation for the differences between groups in motor skills, IQ, and other behavioural and developmental characteristics is a significant adverse effect of sodium deficiency of growth and development of the central nervous system, and that appropriate steps should be taken to optimise sodium intake of very premature infants during the first 2 weeks of postnatal life, and to prevent hyponatraemia, in accordance with previously published guidelines.[3 5]

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