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

J Al-Dahhan, L Jannoun, G B Haycock

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.
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)\(^\text{13}\) 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.

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

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

Where applicable, values are median (range). There were no significant differences between the groups.

SVD, Spontaneous vaginal delivery; LSCS, lower segment caesarean section; EBM, expressed breast milk.

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

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

Values are mean (SD).

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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 \(\chi^2\) 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.
DISCUSSION

Several studies have found evidence of impaired motor function in infants born very prematurely, with the degree of impairment in some of these, but not all, being inversely correlated with birth weight. Levene et al 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 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++, 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 (15–18). In a later paper, Lucas et al 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, or their own mothers’ milk, compared with those fed standard term formula. The findings of Murphy et al 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 (15–18 20 26 28) (for review see Haycock27). One study 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 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 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.23 24
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 cardio-pulmonary function and, possibly, an increased risk of chronic lung disease of prematurity. Delaying the onset of sodium supplementation until 4–5 days of age or until a measured weight loss of 6% has occurred 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.

REFERENCES

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- Dietary salt and development in premature babies