Relationships between early neonatal nutrition and neurodevelopment at school age in children born very preterm

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Contributors' Statements

Anna Tottman: Dr Tottman conceptualized and designed the study, coordinated and performed data collection, performed initial data analysis, drafted the initial manuscript and approved the final manuscript as submitted.

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Jane Harding: Distinguished Professor Harding conceptualized and designed the study, supervised data analysis, critically reviewed and revised the manuscript and approved the final manuscript as submitted.

Abstract

Objectives: To determine whether a new nutrition protocol designed to increase early protein intakes while reducing fluid volume in infants born very preterm was associated with altered neurodevelopment and growth in childhood.

Methods: A retrospective, observational cohort study of children born <30 weeks' gestation or <1,500 grams and admitted to the neonatal unit, National Women's Hospital, Auckland, NZ, before and after a change in nutrition protocol. The primary outcome was neurodevelopmental impairment at 7 years (any of Wechsler Intelligence Scale for Children full scale IQ<85, Movement Assessment Battery for Children-2 total score $\leq 5^{th}$ centile, cerebral palsy, blind or deaf requiring aids). Outcomes were compared between groups and for the overall cohort using generalised linear regression, adjusted for sex and birth weight z-score.

Results: Of 201 eligible children, 128(64%) were assessed (55/89(62%) exposed to the old nutrition protocol, 73/112(65%) to the new protocol). Children who experienced the new protocol received more protein, less energy and less carbohydrate in postnatal days 1-7. Neurodevelopmental impairment was similar at 7 years (30/73 (41%) vs 25/55 (45%), adjusted odds ratio (AOR) (95% confidence interval) 0.78(0.35-1.70), P=0.55), as was the incidence of cerebral palsy (AOR 7.36(0.88–61.40), P=0.07). Growth and body composition were also similar between groups. An extra one $g.kg^{-1}$ parenteral protein intake in postnatal days 1-7 was associated with a 27% increased odds of cerebral palsy (AOR 1.27(1.03–1.57), P=0.006).

Conclusions: Higher early protein intakes do not change overall rates of neurodevelopmental impairment or growth at 7 years. Further research is needed to determine the effects of higher early parenteral protein intake on motor development.

What is known?

- Recommended protein intakes for preterm neonates have increased as a strategy to combat neonatal growth faltering.
- Studies of increased neonatal protein intakes have shown mixed short-term outcomes.
- Few neonatal nutrition studies report long-term neurodevelopmental and growth outcomes.

What is new?

- A change in neonatal nutrition protocol resulting in higher neonatal protein and lower energy intakes was not associated with altered neurodevelopmental outcomes at 7 years' corrected age.
- Growth and body composition at 7 years' corrected age was also similar in children born before and after the change.
- On exploratory analysis, higher early parenteral protein intake and higher protein-to-energy ratios were associated with more cerebral palsy.

Introduction

Infants born very preterm frequently require a period of parenteral nutrition immediately after birth; however, the ideal composition of that nutrition is not yet clear. Supplied protein intakes do not match *in utero* intakes for many days after birth [1], and increasing early neonatal protein intakes may mitigate postnatal growth faltering [2, 3], a condition associated with adverse neurodevelopmental outcomes in later life [4]. Although higher early enteral protein intakes may be beneficial [5], the results of contemporary studies of higher parenteral protein intakes in the very preterm population are mixed [3, 6-9], including reports of worsened growth and neurodevelopmental outcomes [10, 11]. This study aims to determine whether a change in neonatal parenteral nutrition protocol intended to increase early protein intake and reduce fluid volume intake was associated with altered neurodevelopmental outcomes in 7 year old children born very preterm and, if so, to determine which individual nutritional components contributed to this difference.

Methods

Eligible participants were born before (July 2005-December 2006) and after (January 2007-October 2008) a change in the neonatal parenteral nutrition protocol and admitted to the Neonatal Intensive Care Unit of National Women's Hospital, New Zealand within 24h of birth. They were identified from 3 sources: children who had been recruited as neonates to a randomized controlled trial (RCT) of tight glycemic control for neonatal hyperglycemia [12]; children who had been matched to RCT participants as non-hyperglycemic preterm controls, and children included in a contemporaneous audit of the effect of the change in nutrition protocol on neurodevelopmental outcomes at 2 years' corrected age [13]. We excluded infants who did not survive to 7 years' corrected age, those exposed to both old and new nutrition

protocols within the first 7 days, and those who were transferred in to NICU after 24 hours or transferred out prior to postnatal day 7.

The study received approvals from the Northern B ethics committee (NTY/12/05/035), and from the Auckland District Health Board (ADHB 5486).

Eligible participants were traced and invited to take part in an assessment at the Liggins Institute, University of Auckland, New Zealand. Assessment procedures have been described previously [14] and included: Wechsler Intelligence Scale for Children 4th Edition (Australian) (WISC IV); Movement Assessment Battery for Children 2nd Edition (MABC-2); Beery-Buktenica test of visual motor integration administered by a trained assessor (all Pearson, Texas, USA); neurological examination and functional motor assessment [15] by a Pediatrician; visual acuity assessment by an optometrist; growth measures using standard techniques with results averaged and converted to z-scores, and body composition using dual x-ray absorptiometry (Lunar Prodigy utilising enCORE software, both GE Healthcare, USA). Although exposure to old and new nutritional protocols was birth-date dependent and thus not able to be fully concealed, assessments were performed blind to children's actual neonatal nutritional intakes.

All actual enteral and parenteral fluid intakes (excluding blood products) for the first 28 days after birth were collected from the medical record, and macronutrient intakes per kilogram per day calculated for each infant using the reference data given in Table, Supplemental Digital Content 1 (online) and the latest, highest weight. The calendar day of birth was excluded from further analysis due to its variable duration, and fluid, macronutrient and energy intakes were then averaged for days 1-7 (week 1), days 1-14 (fortnight 1) and days 1-28 (month 1). In addition, for the exploratory analyses, total fluid, macronutrient and energy intakes per kilogram were summed for days 1-7 and days 1-14.

Neonatal weight, length and head circumference measures were converted to z-scores [16]. Neonatal data were used to determine socioeconomic status [17] and the clinical risk index for babies (CRIB-II) score [18], and details of the following neonatal morbidities were collected: intraventricular hemorrhage (grade III/IV) [19]; necrotizing enterocolitis (Bell stage ≥2) [20]; retinopathy of prematurity (stage III/IV) [21]; chronic lung disease [22], major neonatal surgery [22], and sepsis [22].

The primary outcome was neurodevelopmental impairment at 7 years' corrected age, defined as any of: full scale IQ <85 (-1 SD); MABC-2 score ≤5th centile; cerebral palsy; blindness (presenting visual acuity of 6/60 or worse in the best eye), or deaf requiring aids. Because the original audit inclusion criteria selected for survivors, death was not included in the primary outcome. Secondary outcomes included individual components of the primary outcome, growth, and body composition.

Statistical analyses were performed using SAS v.9.4 and JMP v.11.2.0. Significance level was set at 5% with no adjustment for multiple comparisons, and no interpolation of missing data. Continuous variables were summarised using mean (standard deviation) or median (inter-quartile range), and compared between groups using two-sample t-test or Wilcoxon test for non-normal data. Categorical variables were summarised as frequencies and percentages, and compared between groups using Chi-square test or Fishers' exact test for cells with counts <5.

Prior to analysis, we considered potential confounders likely to be strongly associated with the outcome of neurodevelopmental impairment. Blinded comparison of baseline characteristics between groups showed that sex (female/male) and birthweight z-score differed by >10% between groups and were thus included as covariates in adjusted analyses. Outcomes assessed at 7 years' corrected age were compared between groups using

generalised linear regression models with an appropriate link function, both unadjusted and adjusted. Results are presented as mean differences for continuous variables, or odds ratios (OR) for categorical variables with 95% confidence intervals (CI). In the primary analysis, the presence of twins in the cohort was considered as a cluster effect using generalised estimating equations. In pre-specified exploratory analyses, relationships between actual neonatal nutritional intakes and neurodevelopmental outcomes were assessed for the whole cohort using generalised linear regression models, adjusted for multiple birth (yes/no), sex, gestational age (in weeks), birthweight z-score and study eligibility arm (RCT participants randomized to tight glycemic control vs. RCT participants randomized to standard glycemic control vs. others).

Results

Of 536 infants <1500 grams or <30 weeks' gestation admitted to NICU from July 2005–October 2008, 201 were eligible for inclusion in this study. Assessments could not be performed in 73/201 (36%) children (see Figure, Supplemental Digital Content 2: Flow diagram of study participants), resulting in the primary outcome of neurodevelopmental impairment being available for 55/89 (62%) of children exposed to the old nutrition protocol and 73/112 (65%) of those exposed to the new nutrition protocol.

In infants exposed to the old nutrition protocol, those who were assessed at 7 years' corrected age (OldPro) were more likely to be from the least deprived socioeconomic (assessed 7/55 (13%) v not assessed 0/34 (0%), $p<0.05$) and to have a smaller crown-heel length at birth (cm, mean ± SD; assessed 34.5 ± 3.1 v not assessed 36.0 ± 3.3, $p<0.05$) than infants who were not assessed. In infants exposed to the new nutrition protocol, those who were assessed (NewPro) were more likely to have a mother who identified as NZ European (assessed 30/73 (41%) v not assessed 10/39 (26%), $p<0.05$) and smaller head circumferences at birth (cm,

mean ± SD; assessed 24.5 ± 1.9 v not assessed 25.4 ± 2.1, p<0.05) than those who were not assessed. NewPro infants were similar to OldPro in gestational age, sex, CRIB-II score, size at birth and at 36 weeks' post menstrual age, neonatal morbidities and receipt of parenteral nutrition (Table 1). NewPro infants were around 25% less likely to have neonatal hyperglycemia, but not different rates of insulin treatment. Full enteral feeds were achieved at a median of 10 days in both groups (Table 1). In week 1, NewPro infants received a mean of 0.4 $g.kg^{-1}.d^{-1}$ more protein, 1.8 $g.kg^{-1}.d^{-1}$ less carbohydrate and 4 $kcal.kg^{-1}.d^{-1}$ less energy than OldPro infants. In month 1, NewPro received a similar amount of protein, but less fat, carbohydrate and energy than OldPro. (Table 2)

The primary outcome of neurodevelopmental impairment was found in 55/128 (43%) children assessed, and was not different between groups (Table 3). NewPro children were almost half as likely as OldPro to have a WISC-IV FSIQ score <85 (adjusted OR (95% CI) 0.52(0.23-1.17)), but this difference did not reach statistical significance (P=0.12) (Table 3). Scores for FSIQ and all subdomains were higher in the NewPro group, but only that for working memory score reached statistical significance (adjusted mean difference (95% CI) 6.32(1.15-11.50) P=0.02).

Cerebral palsy tended to be more common in NewPro (9/73 (12%)) than OldPro children (1/55 (2%)), but this difference did not reach statistical significance (AOR(95% CI) 7.36(0.88-61.40)P=0.07) (Table 3). Children with cerebral palsy had GMFCS ≤2 in all but 1 case (Table 3). NewPro and OldPro groups had similarly high rates of motor impairment, with 55/128 (43%) of the cohort having MABC-2 total scores at or below the referent 15^{th} centile (Table 3).

At 7 years' of age, the cohort had an average weight of 25.2±6.9 kg and 29/128 (23%) were overweight or obese. Weight, length and head circumference, their respective z-scores, and

the incidence of abnormal BMI were similar in NewPro and OldPro groups Table, Supplemental Digital Content 3. There were no differences in body composition among the 124 (97%) children who underwent dual x-ray absorptiometry Table, Supplemental Digital Content 3.

For the cohort as a whole, exploratory analyses showed that there were no associations between total intake of any macronutrient and neurodevelopmental impairment or WISC FSIQ score <85 (Table 4). In the first 14 days, increasing total fat, carbohydrate and energy intakes were associated with reduced odds of having an MABC-2 score $\leq 5^{th}$ centile, but higher protein-energy ratio was associated with triple the odds of having an MABC-2 score $\leq 5^{th}$ centile (Table 4). Parenteral protein intake in the first 14 days was also associated with an increased risk of MABC-2 score $\leq 5^{th}$ centile, but enteral intakes of protein, fat and carbohydrate in days 1-7 and days 1-14 were all associated with reduced odds of this outcome. Greater total and parenteral protein intakes in the first 7 days and higher protein-energy ratios in days 1-7 and 1-14 were associated with an increase in the odds of cerebral palsy. Intake of other macronutrients was not associated with cerebral palsy, and enteral feeding did not appear to have any protective effect (Table 4).

Discussion

The introduction of a new nutrition protocol which resulted in greater protein intake but reduced intake of carbohydrate and energy in the first week was not associated with change in the overall rate of neurodevelopmental impairment, growth or body composition at 7 years in this cohort of children born very preterm. Further analysis of infants' actual nutrient intakes showed no associations between intake of any macronutrient and cognitive impairment, but an association between early protein intake and motor impairment and cerebral palsy. Increased enteral intakes were associated with a reduced likelihood of

neurodevelopmental impairment, including motor impairment, but not cognitive impairment, or cerebral palsy.

The change in the nutrition protocol was originally designed to increase the protein intake, and reduce the fluid volume intake of extremely preterm babies in accordance with international recommended daily intakes [23]. Decreased energy, carbohydrate or fat intake was not intended, but occurred as a consequence of the reduction in fluid volume. Despite the reduction in energy intake we did not see any differences in weight, height or head circumference, nor measures of body composition, between OldPro and NewPro groups at 7 years' corrected age, suggesting that any potential growth alterations do not persist into childhood.

Our finding of an association between increased protein intake, and particularly parenteral protein intake, and increased rates of cerebral palsy and motor impairment, was unexpected, and was reflected in the non-significantly higher rate of cerebral palsy in the NewPro group. Of note, this was not due to due to a notably high rate in the NewPro group (12%), but rather, a rate in the OldPro group (2%) that was lower than expected for such a preterm population [24].

Despite this, the overall percentage of children with motor impairment was not different in children exposed to the different nutritional protocols. Children with mild cerebral palsy had similar MABC-2 motor scores to those without cerebral palsy but with motor impairment, suggesting that motor outcomes lie on a continuum. As clinically detectable neurological abnormality was used to define cerebral palsy, it is possible that those children with mild cerebral palsy have similar functional outcomes to children without neurological signs but with motor impairment. Conversely, it is clear that a substantial group of children born very preterm experience significant motor difficulties in childhood and do not have a diagnosis of

cerebral palsy, a finding that has also been reported in a large international cohort of 11 year olds born at very low birth weights [25].

Randomized trials of early parenteral protein intakes have shown short-term growth outcomes that are better [3], unchanged [26] or worsened [11] in the groups receiving the higher early parenteral protein loads. A study of 61 ELBW infants randomized to receive higher (starting at $2g.kg^{-1}.d^{-1}$) or standard (starting at $0.5g.kg^{-1}.d^{-1}$) parenteral protein intakes showed an increase in chronic lung disease, lower z-scores for weight, length and head circumference, and lower mental development scores at 18 months in the group receiving higher early parenteral protein [10]. Our finding on exploratory analysis that higher early parenteral protein intake may be specifically associated with impaired motor function and cerebral palsy at 7 years' corrected age is in keeping with the findings of a small RCT of parenteral versus enteral nutrition in preterm piglets, where piglets randomized to parenteral nutrition showed a significant decrement in motor function after 3 days, and reduced white matter myelination and smaller cerebellar weights at day 10 [27].

Our observation of increased motor impairment and cerebral palsy in association with higher parenteral protein intakes may reflect a potential imbalance in individual amino acids. We used a commercial amino acid preparation based on TrophAmine (B.Braun, Pennsylvania, USA), containing relatively high arginine concentrations. Arginine stimulates pancreatic insulin secretion, is associated with blood glucose control in preterm infants receiving parenteral amino acid solutions [28], and may be responsible for the decrease in hyperglycemia we have previously reported in a larger neonatal cohort exposed to this change in nutrition protocol [29]. However, in excess, arginine concentrations are associated with progressive spasticity and motor impairment [30]. There is very little literature on the normal amino acid profiles of well preterm infants, and formulations of parenteral amino-acid solutions developed to match amino acid profiles from term infants [31] may not be appropriate for the

very preterm population. The ideal composition of amino acids used in neonatal parenteral nutrition is not known, and trials of parenteral nutrition using short-term growth outcomes as a primary endpoint may miss important long-term neurological effects.

It is possible that our finding of an apparently protective effect of enteral nutrition for motor outcomes may merely reflect that well babies are easier to feed. However, the strong association between enteral intakes of all macronutrients on days 1-7 and a reduced risk of neurodevelopmental impairment at 7 years suggests that enteral feeding is not merely a marker for a less sick infant, as unit policy was to give only maternal breastmilk during this period, and thus very early enteral intakes are likely to reflect maternal supply rather than infant feed tolerance. Enteral feeding is associated with production of incretins and maturation of the enteroinsular axis [32,33], stabilization of blood glucose concentrations [28], and enhanced integrity of the intestinal mucosa [34], an important component of the immune system [35]. It is not clear which, if any, of these effects, may be associated with improved motor outcomes.

We have previously reported that in this cohort at 18 months' corrected age there were no differences between groups in cognitive or motor outcomes, but that protein intake in the first two weeks was positively related to Bayley cognitive and motor but not language scores[13]. At that time we did not distinguish enteral from parenteral intakes, and the contrasting relationships between these two intake routes and developmental outcomes may have contributed to that finding. The limitations in the predictive value of early Bayley assessments for later developmental achievements are also well recognised.

The major limitation of this study is the non-contemporaneous nature of the cohorts which increases the possibility of bias as there may have been other changes to neonatal care during the study recruitment period which may have affected the study outcomes. There may also

have been more children who survived with cerebral palsy in the new protocol era. The association of macronutrient intakes with motor outcomes was found in a pre-specified exploratory analysis. This analysis should be regarded as hypothesis generating and requires further study in randomised controlled trials. There was also a relatively small sample size, restricted by the original numbers recruited into the RCT and nutritional audits, and hence limited power to detect small differences in neurodevelopmental outcomes. Nevertheless, this study represents one of the largest cohorts reported in a neonatal nutrition study, and is one of very few where assessments have been made in mid-childhood. Our findings are also made more robust by the collection and interrogation of actual nutritional intakes, regardless of nutritional protocol exposure.

In summary, a change in nutritional protocol which resulted in higher protein and lower carbohydrate and energy intakes in early life did not change the overall rate of neurodevelopmental impairment at 7 years. On exploratory analysis, early parenteral protein intakes were associated with cerebral palsy, whereas higher early enteral intakes appeared protective against motor but not cognitive impairment. There is an urgent need for randomized controlled trials of different early neonatal protein intakes with growth and neurodevelopmental outcomes assessed at least into mid-childhood.

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Figures and supplemental digital content legends

Figure, Supplemental Digital Content 1: Flow diagram of study participants

Table, Supplemental Digital Content 2: Macronutrient reference values

Table, Supplement Digital Content 3: Growth and anthropometry in children exposed to the old or new neonatal nutrition protocols who were assessed at 7 years

STROBE Checklist

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Reported on page no
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6,8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5,6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6,
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	SDC 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 2
		(c) Summarise follow-up time (eg, average and total amount)	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2, 3
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction

with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.