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The association between restricted intra-uterine growth and inadequate postnatal nutrition in very-low-birth-weight infants and their neurodevelopmental outcomes: a 50-month follow-up study

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Abstract

Inadequate nutrition during a critical period of development – as is the case during gestation and the first days of life, especially in very-low-birth-weight (VLBW) infants, can impact on neurodevelopment and favour co-morbidities. In this study, we evaluate how neurodevelopment may be affected by intra-uterine growth (IUGR) restriction and by an inadequate intake of nutritional energy during the early neonatal period. A longitudinal cohort study was conducted to analyse the nutritional contributions received during the first week of life, among a population of 396 VLBW infants. Motor, cognitive, sensory and behavioural development was assessed at 14, 25, 33 and 50 months. The association between IUGR, postnatal energy restriction and neurodevelopment was examined using multivariate logistic regression techniques. Mild cognitive delay was observed in 35·6 % of neonates with IUGR and in 24 % of those with appropriate birth weight. IUGR is associated with behavioural disorder (OR 2·60; 95 % CI 1·25, 5·40) and delayed cognitive development (OR 2·64; 95 % CI 1·34, 5·20). Energy restriction during the first week of life is associated with visual deficiency (OR 2·96; 95 % CI 1·26, 6·84) and cerebral palsy (OR 3·05; CI 95 % 1·00, 9·54). In VLBW infants, IUGR is associated with behavioural disorder, while postnatal energy restriction is significantly associated with motor disorder, infantile cerebral palsy and sensory disorder.

Key words: **Nutrition: Newborn: Very low birth weight: Neurodevelopment: Intra-uterine growth restriction**

Long-term follow-up studies indicate that very-low-birth-weight (VLBW) newborns are at increased risk of long-term morbidity due to prenatal or neonatal problems. Thus, 15–30 % of VLBW infants have a birth weight below the 10th percentile for their gestational age (i.e. they are small for gestational age - SGA), while infants who experience intra-uterine growth restriction (IUGR) are considerably more liable to mortality and morbidity[1–4]. IUGR is a clinical concept, describing newborns with malnutrition and IUGR, regardless of their birth weight percentile, and resulting from maternal, placental, fetal or genetic factors. Various maternal factors, such as age, health, behavioural habits and infection, may affect the growth of the fetus and provoke IUGR. A mismatch between the placental supply and the nutritional demands of the fetus can also result in IUGR. In some cases, too, fetal malformations, congenital metabolic errors or chromosomal abnormalities may produce IUGR[1].

The Nutrition Committee of the American Academy of Pediatrics recognises the importance of providing premature newborns with adequate nutrition during the first days of life, with contributions of energy and macronutrients similar to those received by the intra-uterine fetus[5,6]. However, nutritional energy deficits inevitably occur in some cases, especially during the first week of life[7], often due to severe prematurity-related conditions such as intraventricular haemorrhage, necrotising enterocolitis, persistent ductus arteriosus, periventricular leucomalacia or bronchopulmonary dysplasia[8,9] or to other factors such as poor tolerance of enteral nutrition, concern about the parenteral tolerance of high contributions of macronutrients (proteins, carbohydrates and lipids) or the need to restrict parenteral fluid intake, as part of persistent ductus arteriosus therapy.

Some studies have reported that IUGR infants are more likely to present inadequate visual and psychomotor development[10,11], while others have associated prematurity

Abbreviations: IUGR, intra-uterine growth; MDI, mental development index; PN, parenteral nutrition; SGA, small for gestational age; VLBW, very-low-birth-weight.

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in fetuses affected by IUGR with hyperactivity disorders, but with little impact on cognitive development[12]. Furthermore, imaging tests in SGA infants with IUGR have revealed structural alterations and lower brain volume than in appropriate-birth weight premature infants[13].

After preterm delivery, the nutritional and energy contributions to the fetus from the placenta are abruptly interrupted, provoking a nutritional and energy deficit in the VLBW newborn at a crucial moment, which may influence the development of the brain and its glial cells. Variations in the establishment of early nutrition – possibly due to enteral intolerance, restricted fluid intake or the non-availability of central venous access – might affect development of the brain[14].

Increased energy and protein intake in the first week of life has been associated with improved neurodevelopmental outcomes in VLBW infants[15]. In this respect, too, Schneider *et al.*[16] observed that increased energy intake during the first 2 weeks of life of VLBW infants is related to better brain development, of both white and grey matter. Other authors have observed that postnatal growth restriction, caused by a nutritional deficit, is associated with alterations in the cortical microstructure[17].

Our study aim is to evaluate the impact on neurodevelopment in VLBW infants of IUGR and of inadequate nutrition during the early neonatal period.

Subjects and methods

This retrospective, longitudinal cohort study was conducted of neonates born at the San Cecilio Clinical Hospital (Granada) between January 2008 and December 2017. The study protocol was approved by the Ethics Committee of the hospital, and all current regulations regarding data confidentiality were respected.

Inclusion and exclusion criteria

All newborns weighing <1500 g admitted to the neonatal intensive care unit during the study period were included in our initial analysis. Subsequently, each child was followed up in Neonatology and Neurology consultations. Infants who died in the first 28 d of life and those transferred to other hospitals were excluded from the analysis. Also excluded were neonates with congenital infections, proven genetic alterations, major malformations and an incomplete record of nutritional intake during the first week of life, together with those who did not attend the scheduled follow-ups. Fig. 1 shows the flow diagram representing the process applied for patient recruitment and inclusion.

Anthropometry

Table 1 shows the weights and *z*-scores obtained at birth and during the first week of life. Fenton tables were used to calculate the *z*-scores[18]. IUGR is defined as a reduced rate of weight increase, resulting in a weight below the 10th percentile for gestational age[19]. In our sample, all cases of IUGR were diagnosed by intra-uterine ultrasound study. In accordance with Alexander *et al.*[20], SGA is defined as birth weight below the 10th percentile for gestational age.

Nutritional management

The nutritional strategy was applied and the neonates' fluid intake controlled in accordance with the standard protocol of our neonatal unit and with the recommendations of the Nutrition and Metabolism Group of the Spanish Neonatology Society[21,22]. In all cases, 1·2 μm filters were used for parenteral nutrition (PN) (Pall, Medical). Two changes were made to this nutritional practice during the study period. In April 2011, first-day PN (early PN) began to be applied with an amino acid

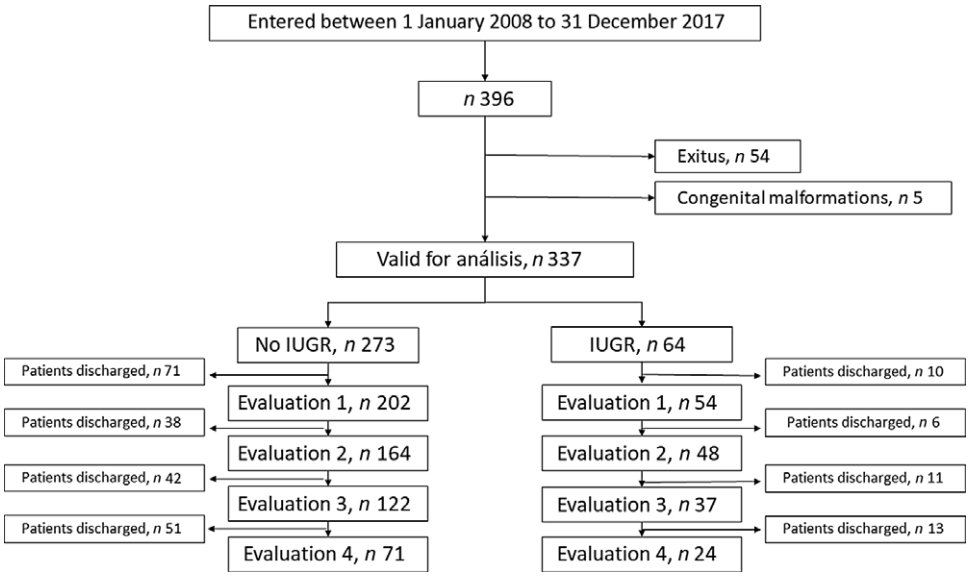

Fig. 1. Flow diagram for the very-low-birth-weight (VLBW) newborns included in the study.

Table 1. Pregnancy, neonatal and nutritional characteristics (Number and percentages; median and interquartile range)

Characteristics	No IUGR (*n* 273)		IUGR (*n* 64)		*P*-value
	n	%	*n*	%	
Maternal					
IVF	48	17·6	6	9·4	0·11
PIH	14	5·1	7	10·9	0·08
Chorioamnionitis	36	13·2	2	3·1	0·02
Antibiotics	105	38·5	8	12·5	<0·001
Glucocorticoids	236	86·8	52	81·3	0·25
PPROM	67	24·5	4	6·3	0·001
Gestation (w)					<0·001
Median	29		32		
IQR	28, 31		30, 33		
Gestation ≤ 27 w	65	23·8	8	12·5	0·04
Twin birth	115	1·42	20	31·3	0·11
Caesarean section	213	78·0	60	93·8	0·004
SGA	14	5·1	62	96·8	0·001
Neonatal					
Birth weight (g)					0·001
Median	1240		1111		
IQR	1020, 1463		902, 1290		
Birth weight (*z*-score)					<0·001
Median	−0·27		−1·69		
IQR	−0·71, 0·22		−2·03, −1·47		
Weight 7 d (*z*-score)					<0·001
Median	−0·96		−2·18		
IQR	−1·34, −0·58		−2·51, −1·74		
Male sex	148	54·2	33	51·6	0·70
Apgar < 7 at 5 min	67	26·5	17	27·9	0·82
CRIB score	2	1, 6	2	1, 5·7	0·65
Milk breast-feeding*	137	62·3	39	66·1	0·58
Neonatal co-morbidities					
BPD	120	44·1	21	32·8	0·09
PDA	52	19·1	6	9·4	0·06
IVH (Grades I–II)	39	14·3	1	1·6	0·005
IVH (Grades III–IV)	11	4·0	1	1·6	0·33
PVL	2	0·7	1	1·5	0·82
NEC (Grade ≥ 2)	26	9·5	6	9·4	0·97
Late onset sepsis	60	22·0	13	20·3	0·77
Neonatal nutritional intake in the 1st week					
Energy (kcal/kg per week)					0·43
Median	456·4		467·0		
IQR	385, 515		402, 531		
Lipids (g/kg per week)					0·10
Median	12·3		13·4		
IQR	7·7, 15·2		9·3, 16·5		
Carbohydrates (g/kg per week)					0·25
Median	70·9		72·5		
IQR	63·9, 77·6		65·9, 80·1		
Proteins (g/kg per week)					0·73
Median	15·7		15·2		
IQR	11·5, 18·8		11·4, 19·1		

BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus; IVH, intraventricular haemorrhage; ROP, retinopathy of prematurity; NEC, necrotising enterocolitis; CRIB, clinical risk index for babies; SGA, small for gestational age; PVL, periventricular leukomalacia.

* Supplemented by <25 % of the weekly volume with premature formula milk, IUGR, intra-uterine growth retardation; IVF, *in vitro* fertilisation; PIH, pregnancy induced hypertension; PPROM, preterm pre-labour rupture of membranes; IUGR, intra-uterine growth restriction (decrease in the rate of weight increase that manifests as weight below the 10th percentile for gestational age).

solution (2 g/kg) and with glucose at 5 mg/kg/min. Previously, amino acid had not been supplied during the first hours of life. This change, which aligned our action protocols with international recommendations, increased the newborns' energetic intake in the first week of life and, secondarily, enabled us to assess the energy repercussions more effectively. The second modification concerned the lipid emulsion used. In July 2016, SMOFlipid (Fresenius Kabi) was introduced, replacing intralipid (Fresenius Kabi) as an emulsion commonly used in PN. The repercussions of this change with respect to energy intake are taken into account in our analysis of the results.

The normal procedure during the first days of life is to complement enteral nutrition with PN when complete enteral nutrition cannot be established. The daily requirements of liquids, proteins and lipids are calculated daily. At our hospital, breast milk composition is determined according to the Standardized Reporting of Neonatal Nutrition and Growth checklist, and formula composition is assessed according to

commercial notifications[23]. In all cases, the aim is that during the first week of life the minimum nutritional requirements to ensure growth should be met, according to standard recommendations[24]. For the purposes of the present study, the inputs of liquids, energy, proteins, carbohydrates and lipids during the first week of life were recorded.

Since January 2008, the neonatal intensive care unit has prospectively recorded in an Excel database the daily enteral and parenteral nutritional intake of all VLBW admitted, specifying the intake per kg body weight of energy, proteins, carbohydrates and fats. The time of initiation and type and volume of enteral nutrition are also recorded.

Low energy intake

In our sample, energy intake below the 25th percentile was assumed to represent energy restriction, and so this was chosen as the cut-off point for increased risk of neurological disorder. This value is equivalent to about 60 % of the recommended energy intake during the first week of life.

Morbidity

In accordance with the thresholds proposed by National Institute of ChildHealth and Human Development (NIHCD)[25] and by Jobe and Bancalari[26], bronchopulmonary dysplasia is defined as a need for supplemental oxygen > 21 % at 28 d of life and/or a need for supplemental oxygen > 21 % or for positive airway pressure at 36 weeks' corrected gestational age.

A diagnosis of clinical sepsis is made when a Prediction of nosocomial sepsis (NOSEP)-1 score > 8 is recorded. On this scale, the presence of c-reactive protein (CRP) > 0·014 g/l is assigned five points; that of neutrophils > 50 %, three points; that of thrombocytopaenia < 150×10^9/l, five points and that of fever > 38·2ºC, five points[27]. The clinical risk index for babies II score for each newborn was performed using the following variables: sex, gestational age (in weeks), birth weight (in grams) and excess base. The total clinical risk index for babies II score (range 0 to 27) was calculated[28].

The diagnosis and staging of retinopathy of prematurity were performed following a retinal examination before discharge from the neonatal unit[29,30].

Persistent ductus arteriosus is diagnosed by Doppler ultrasound and treated when clinical repercussions are observed or when the diameter is greater than 2 mm.

The diagnosis of intraventricular haemorrhage is based on Papile's classification[31]. All neonates in this study received a transfontanellar ultrasound examination on the third day of life and every week thereafter.

For the diagnosis of necrotising enterocolitis, patients are classified according to Bell's criteria[32]. Cases classified as spontaneous intestinal perforations were excluded from this diagnosis.

Psychomotor and sensory development

At our hospital, this parameter is monitored during neuropaediatric consultation. For each infant included in the study, four such reviews were conducted, at the following times (median value and interquartile range): Review 1 at 13 months[12], Review 2 at 24 months[19], Review 3 at 36 months (29·5–39) and Review 4 at 48 months (36·5–50). For the present study, motor alterations are classified as (a) mild motor disorder, which includes motor coordination disorders that are not the consequence of cognitive or neurological alterations evidenced by imaging tests; this category includes fine and gross motor abilities that are significantly below the level expected; (b) monoparesis, i.e. motor alteration affecting a single limb, muscle or muscle group; (c) hemiparesis, i.e. motor alteration affecting an arm or leg on the same side of the body and (d) tetraparesis, i.e. motor alteration affecting all four limbs. Visual and auditory sensory capacities were determined by measuring the evoked potentials. Motor, coordination, language, social and cognitive development was evaluated and the mental development index (MDI) scored by means of the Brunet-Lezine and Bayley III scale. The level of cognitive delay was determined according to the mental age derived from the MDI and the resulting intelligence quotient, as follows: mild delay (IQ: 50–70), moderate delay (IQ: 35–50) or severe delay (IQ: 20–35), in accordance with the *International Statistical Classification of Diseases and Related Health Problems (ICD, Ed. 10)*. When two or more motor or sensory impairments were detected, this was considered a multiple deficiency. Behavioural disorders were assessed by the CUMANIN questionnaire and the Wechsler Intelligence Scale. Cerebral palsy is a set of developmental disorders affecting movement and posture, thereby limiting activity. The condition is attributed to a non-progressive aggression on the developing brain, during the fetal period or early years of life, and is frequently associated with sensory disturbances[33]. When detected, the presence of epilepsy, defined as repeated seizures with alterations in electrical activity in the electroencephalogram, was also recorded.

Statistical analysis

The descriptive data were summarised using medians (p50) and the interquartile range (p25–p75) for the continuous values and frequency distribution for the categorical ones. Univariate comparisons of the continuous variables were performed using the Mann–Whitney test and of the categorical ones by the χ^2 test. The risk of motor, visual and hearing disorders, delayed cognitive development, behavioural disorder, multiple deficiency, cerebral palsy and epilepsy was first assessed by univariate regression analysis and then by multivariate logistic regression analysis. Birth weight is strongly associated with gestational age and so this variable was not taken into account, in order to avoid over-fitting phenomena that might bias the associations obtained in the regression analysis. No adjustment was made for the CRIB index because this was calculated from gestational age, weight and male sex, among other variables, and these were previously taken into account in the regression analysis. The main adjustment factors considered are the co-morbidities of VLBW that are associated with poorer neurological outcomes, especially lower gestational age, late-onset sepsis, bronchopulmonary dysplasia, patent ductus arteriosus, SGA, intraventricular haemorrhage and leukomalacia.

All statistical analyses were performed using IBM SPSS 20.0 for Windows (IBM).

Reporting

The STROBE checklist for reporting observational studies was used[34].

Results

During the period from 1 January 2008 until 31 December 2017, 396 newborns weighing < 1500 g were treated in our neonatal unit. Of these, fifty four died in the neonatal period and five had congenital malformations and were excluded from the study. The remaining 337 newborns were included in our analysis. Among this population, sixty-four infants had experienced IUGR. At birth, sixty two had a birth weight below the 10th percentile and were classified SGA (Table 1). During follow-up, the infants presenting normal development were discharged. Fig. 1 describes the follow-up cohort remaining after each neurological and sensory evaluation. Comparison of the *z*-score variables for weight and gestational age, between the infants discharged and those who remained in the study, at each of the reviews performed, only revealed significant differences for the gestational age variable. In general, the patients with a lower gestational age remained in follow-up for longer.

Table 1 shows the maternal and neonatal characteristics of the study cohort, revealing significant differences between the infants with and without IUGR according to the maternal variables: preterm premature rupture of membranes, chorioamnionitis and maternal antibiotics. In every case, these conditions were more prevalent in the group without IUGR, which we ascribe to the fact that infection and chorioamnionitis are present in about one-third of all cases of prematurity. Mean gestational age in the IUGR group was 32 weeks and delivery by caesarean section often indicated placental insufficiency, resulting in decreased fetal well-being and chronic malnutrition[35]. Among other neonatal co-morbidities observed, the VLBW newborns with appropriate weight had a greater prevalence of grade 1 or 2 intraventricular haemorrhage and a significantly lower mean gestational age. For the remaining neonatal co-morbidities, no significant differences were observed between the study groups.

Following the incorporation of early PN in the standard protocol for the neonatal unit, an increase in average energy intake during the first week of life was observed. Table 1 shows the weight and *z*-score data in this respect. The weight loss during the first week of life was greater among the infants with IUGR, although they received similar energy and macronutrient inputs to those without IUGR.

Table 2 shows the prevalence of neurological abnormalities detected in our study cohort after a mean follow-up of 50 months. Although no significant differences were observed overall, mild motor disorder was present in 10 % of the newborns with IUGR and SGA *v.* 3·2 % of those with appropriate birth weight. Moreover, mild cognitive delay was detected in 35·6 % of the infants with IUGR *v.* 24 % of those with appropriate birth weight. Table 3 shows the OR for neurological disorders in the IUGR neonates who were followed up for 50 months. After adjusting for differentiating maternal variables (Table 1) and for neonatal variables relevant to neurodevelopment, we observed a significant association between IUGR and behavioural disorders (OR 2·60; 95 % CI 1·25, 5·40) and between IUGR and delayed cognitive development (OR 2·64; 95 % CI 1·34, 5·20).

In our study cohort, mean energy intake during the first week of life was 459 kcal/kg/w, with the 25th percentile being 390 kcal/kg/w. In accordance with the method applied in previous studies[36], for the following risk analyses the value of the 25th percentile of energy intake during the first week of life (390 kcal/kg/w) was considered a limit value for low energy intake. As shown in Table 1, there were no differences in energy and macronutrient intake between newborns with or without IUGR. Table 4 describes the risk of neurological alteration associated with low energy intake during the first week of life, in newborns with or without IUGR. Of the 273 newborns with no IUGR, 63 had an energy intake in the first week of life below that of the 25th percentile of the study cohort. Logistic

Table 2. Neurological disorders observed. Average follow-up of 50 months
(Number and percentages)

	No IUGR (*n* 273)		IUGR (*n* 64)		
Neurological alterations	*n*	%	*n*	%	*P*-value
Motor disorders					0·11
Mild motor disorder	8	2·9	6	9·3	
Diparesis	11	4·0	1	1·6	
Hemiparesis	3	1·1	1	1·6	
Tetraparesis	6	2·2	0	0	
Visual disorders	50	18·3	9	14·1	0·39
Hearing disorders	21	7·7	2	3·1	0·19
Delayed cognitive development					0·22
Mild cognitive delay	60	21·9	21	32·8	
Moderate cognitive delay	16	5·9	4	6·3	
Severe cognitive delay	5	1·8	0	0	
Conduct disorders	41	15·0	17	26·6	0·02
Multiple deficiency	14	5·1	2	3·1	0·48
Cerebral palsy	23	8·4	4	6·2	0·54
Epilepsy	17	6·2	1	1·6	0·13

Table 3. Regression analysis for neurological disorders and the existence of IUGR in VLBW newborns. Follow-up until 50 months of age
(Odd ratio and 95 % confidence intervals)

	Unadjusted		Adjusted*	
Neurological alterations	OR	95 % CI	OR	95 % CI
Motor disorders	1·21	0·52, 2·81	3·12	1·14, 8·85
Visual disorders	0·71	0·33, 1·55	1·14	0·47, 2·75
Hearing disorders	0·38	0·08, 1·69	0·56	0·11, 2·75
Delayed cognitive development	1·53	0·85, 2·74	2·64	1·34, 5·20**
Behavioural disorders	2·06	1·07, 3·97***	2·60	1·25, 5·40**
Multiple deficiency	0·58	0·13, 2·66	1·62	0·26, 10·1
Cerebral palsy	0·71	0·23, 2·15	1·93	0·53, 7·08
Epilepsy	0·23	0·03, 1·80	0·46	0·05, 3·95

* Adjusted for chorioamnionitis, antibiotics, PPROM, preterm pre-labour rupture of membranes; gestational age (w); IVH, intraventricular haemorrhage; PVL: periventricular leukomalacia.
** $P \leq 0{\cdot}01$,
*** $P < 0{\cdot}05$.

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Table 4. Neurological disorders associated with low energy intake during the first week of life of very-low-birth-weight (VLBW) newborns with appropriate birth weight. Follow-up to 50 months of age (Odds ratio and 95 % confidence intervals)

	Unadjusted		Adjusted*	
Neurological disorders	OR	95 % CI	OR	95 % CI
Motor disorders	3·89	1·78, 8·50**	2·30	0·88, 5·95
Visual disorders	5·68	2·72, 11·8**	2·96	1·26, 6·84***
Hearing disorders	1·38	0·50, 3·82	0·54	0·15, 1·87
Delayed cognitive development	1·84	0·94, 3·61	1·66	0·82, 3·35
Behavioural disorders	0·66	0·31, 1·43	0·45	0·19, 1·09
Multiple deficiency	7·60	2·52, 22·9**	3·40	0·84, 13·6
Cerebral palsy	5·60	2·27, 13·7**	3·05	1·00, 9·54****
Epilepsy	2·82	1·03, 7·69****	1·49	0·42, 5·31

* Adjusted for gestational age (w), sepsis, bronchopulmonary dysplasia, necrotising enterocholitis ≥ 2 (NEC ≥ 2), persistent ductus arteriosus (PDA), small for gestational age (SGA), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL).** $P \leq 0{\cdot}001$, *** $P \leq 0{\cdot}01$, **** $P < 0{\cdot}05$.

regression analysis was performed to evaluate the risk of specific neurological alterations associated with low energy intake (i.e., < 390 kcal/kg/w) during the first week of life. The OR values obtained, whether unadjusted or following statistical adjustment for variables that may have neurological repercussions (gestational age, sepsis, bronchopulmonary dysplasia, necrotising enterocolitis, persistent ductus arteriosus, SGA, intraventricular haemorrhage or leukomalacia), reveal significant associations between energy restriction in the first week of life and visual disorders (OR 2·96; 95 % CI 1·26, 6·84) and cerebral palsy (OR 3·05; 95 % CI 1·00, 9·54).

Among the full-term VLBW neonates, we observed a significant association between the mental development index at age 13 months and energy intake during the first week of life. However, there was no significant association between this index and protein intake. Lipid intake during the first week of life was significantly associated with the mental development index at age 24, 36 and 48 months (see Fig. 2).

Discussion

Our findings show that the prenatal energy restriction manifested by IUGR is associated with behavioural disorders in the VLBW newborn. Moreover, postnatal energy restriction is

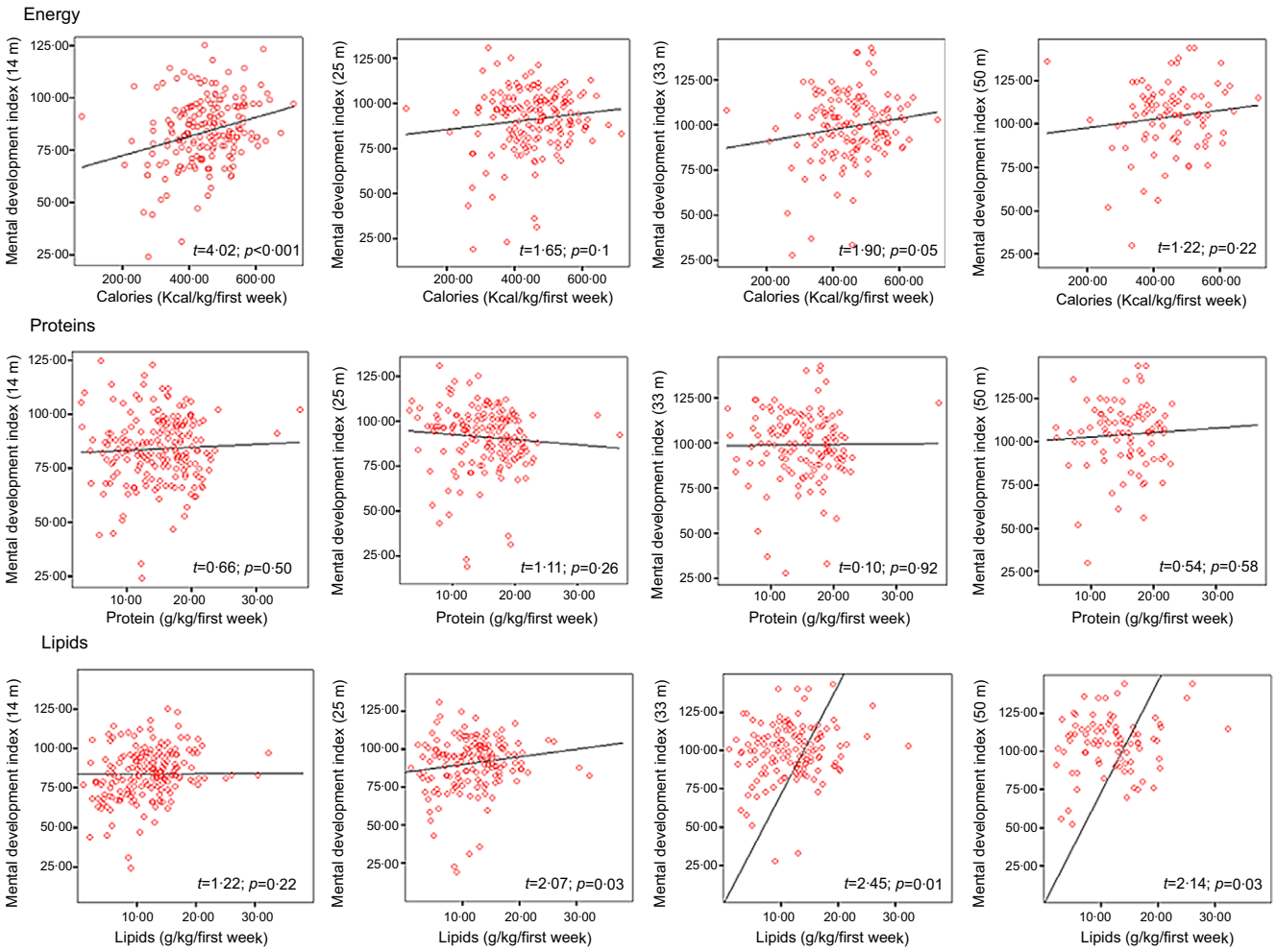

Fig. 2. Regression analysis for the mental development index at 14, 25, 33 and 50 months and the contribution of energy (A), proteins (B) and lipids (C) in the first week of life of very-low-birth-weight (VLBW) newborns with no Intra-uterine growth retardation (IUGR).

significantly associated with motor disorders, infantile cerebral palsy and sensory disorders.

IUGR is defined as the growth rate of a fetus below the 10th percentile of expected growth for that gestational age. An infant is considered SGA when the birth weight is below the 10th percentile. Suboptimal fetal growth is an important cause of perinatal mortality and morbidity. In our study population, all of the VLBW infants with IUGR were SGA.

Postnatal nutritional and energy intake did not vary significantly between VLBW infants with or without IUGR. Nor was it associated with the neurological morbidity observed in our cohort after IUGR. Among the common co-morbidities observed in VLBW infants (Table 1), the only differences observed were in the prevalence of intraventricular haemorrhage grades 1 and 2, which was higher in newborns without IUGR, undoubtedly due to their lower gestational age.

Prematurity in itself does not appear to be associated with higher scores on the attention deficit hyperactivity disorder rating scales. However, prematurity associated with SGA, which is observed after IUGR, is significantly associated with higher attention deficit hyperactivity disorder scores[37]. According to the latter authors, the degree of SGA at birth and IUGR, regardless of gestational age at birth, is related to hyperactivity. On the other hand, attention deficit, which forms part of the attention deficit hyperactivity disorder syndrome, is more strongly related to extreme prematurity[38,39]. Our results corroborate Bickle Graz *et al.*[12], who observed behavioural disorders, especially hyperactivity, in 76 % of SGA VLBW infants. In this respect, too, Silva *et al.*[40] studied newborns with late prematurity and observed no differences in neurodevelopment between SGA infants and those with appropriate birth weight. Finally, Hartkopf *et al.*[41] observed in newborns with late prematurity that the presence of IUGR is associated with cognitive delays and a significantly lower MDI, in comparison with appropriate-birth-weight infants.

After adjusting for differentiating variables, our data also reflect a significant association between IUGR in VLBW infants and their delayed cognitive development. Specifically, the risk of cognitive delay after IUGR is 2·64 (95 % CI 1·34, 5·20) (Table 3).

Stephens *et al.*[15] observed that increased energy and protein intake in VLBW infants during the first week of life are associated with better rates of mental development. On the other hand, Buddhavarapu *et al.*[42] reported that increased protein intake in the first week of life was not associated with better rates of mental development in preterm infants; however, in this study, the group with a 'high' protein intake did not achieve 3·5 g/kg/d until the sixth day of life.

Lacobelli *et al.*[14] recorded a significant association between energy and macronutrient intake during the first weeks of life and brain development. In this study, preterm infants who experienced postnatal growth restriction, possibly due to nutritional deficits, showed poor cortical microstructure development. Lipids and energy contributed more to the beneficial effect of nutrition, with lipids providing a third of total energy intake. It remains to be determined whether the impact of lipids is due to their high energy content (which reduces the energy deficit and the need for protein catabolism) and/or to the provision of fatty acids, especially essential fatty acids. In line with the above-cited studies, our findings show that increased energy intake in the first week of life of VLBW infants is associated with higher scores on the MDI at the age of 18 months, and that lipid intake is significantly associated with the MDI for the first 50 months of life (Fig. 2). In other words, energy restriction in the first week of life can increase the risk of infantile cerebral palsy threefold.

During the period addressed in this study, changes took place in the hospital's nutritional policy, from reliance on PN with soybean oil as the sole lipid contribution (*n*-3: *n*-6, ratio of 1:7) to a diet incorporating SMOFlipid (fish, soya, olive and coconut oil) (*n*-3: *n*-6, ratio of 2:5). In our neonatal unit, the intake of parenteral lipids is normally limited to 3 g/kg/d, in order to avoid possible pro-inflammatory effects from an excessive intake of parenteral lipids. However, the early intake of at least 0·5 g/kg/day of lipids, from the first day of life, is associated with a significant increase in the growth pattern, which is maintained until the 36th week of gestational age[43]. The accretion of lipids in the fetus begins at the 25th week of gestational age, which is why extremely low birth weight newborns have fewer deposits of long-chain PUFA. *n*-3 and *n*-6 fatty acids are essential for brain and retina development, and many studies have associated decreased long-chain PUFA levels in the VLBW newborn with late psychomotor development[44,45]. Our findings show that the MDI may be associated with the contribution of lipids in the first week of life until the age of 50 months (95 % CI 40·7, 59·0) (Fig. 2). In this respect, Moon *et al.*[46] conducted a meta-analysis, following the Cochrane methodology, finding no significant effects of *n*-3 long-chain PUFA supplementation on the MDI or visual acuity of newborns. However, Shultkin *et al.*[47], in a meta-analysis of 33 clinical trials, observed that supplementation of *n*-3 long-chain PUFA in mothers and preterm infants was associated with higher MDI scores and enhanced visual acuity.

The progressive decrease in the number of patients remaining for follow-up, as infants are discharged from hospital following successive reviews, must be considered. This aspect of the study is viewed as a limitation, since it represents a decrease in the statistical power obtained. However, when a subsidiary neurological disorder is ruled out, it is normal for patients to be discharged from clinical follow-up. On the other hand, although intra-uterine malnutrition frequently provokes IUGR, in a small number of cases its cause cannot be established, and this source of bias should be taken into account. Although the present study, based on a retrospective cohort, has evident limitations we believe the data presented provide valuable support for future meta-analysis studies in this field. We are aware that some of the alterations described are not fixed and will evolve or diminish in periods after those considered in our study. Nevertheless, our findings highlight the strength of evidence that energy and protein intake in the first weeks of life is an important factor in the neurological development of the newborn[48].

Conclusions

In VLBW infants, IUGR is associated with behavioural disorders and with poorer cognitive development. Moreover, nutritional

energy restriction during the early postnatal period is associated with visual disorders and can increase the risk of infantile cerebral palsy threefold. Early lipid intake is associated with better MDI scores at 50 months of age.

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