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ORIGINAL ARTICLE

Evaluation of carnitine deficit in very low birth weight preterm newborns small for their gestational age

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Abstract

Objective: To verify whether small-for-gestational-age (SGA) preterm newborns represent a special risk group for carnitine deficiency. Secondary outcome includes assessment of longitudinal differences of total carnitine (TC), free carnitine (FC) and acylcarnitines between SGA and appropriate-for-gestational-age (AGA).

Methods: A retrospective study to evaluate carnitine and acylcarnitines profile on 144 very-low-birth weight newborns (VLBW), classified as AGA ($n = 73$) and SGA ($n = 71$), was performed by tandem mass spectrometry, during their first 5 weeks of life. Carnitine deficiency was defined as FC <40 μmol/L and FC/TC <0.7.

Results: Carnitine deficiency was observed in the two study groups throughout the monitoring period (maximum FC: 36.05 μmol/L in AGA and 32.24 μmol/L in SGA). FC/TC remains under 0.7 in both with progressive improvement. Unlike expected, a comparatively higher value of TC, FC and total acylcarnitines (tAC) was found in SGA during the first 2 weeks, with significant relevance on day 3–5, especially for tAC ($p < 0.001$). The only acylcarnitine with persistently lower value in SGA is C5 ($p < 0.05$ in first 2 weeks).

Conclusions: A carnitine deficiency was demonstrated in all VLBW. Although birth weight restriction has been suggested as a risk factor for impaired carnitine status, in our study, SGA was not related with higher carnitine deficiency.

Keywords

Acylcarnitines, carnitine, small for gestational age, tandem mass spectrometry, very-low-birth weight

History

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Introduction

L-carnitine (LC) (trimethylamino- β-hydroxybutyrate) is present in cells as free carnitine (FC) and acylcarnitine and plays a key role as a carrier of long-chain fatty acids (LCFA) into the mitochondria for β-oxidation. Since the free hydroxyl group from LC can react with different molecules, the acylcarnitines present a broad range of structures. Its ability to carry esterified metabolites makes LC a single molecule, suggesting that the acylcarnitine profile can be a good marker of metabolic status, particularly in pathological conditions.

Intrauterine growth restriction (IUGR) has been defined as the failure of a fetus to reach its genetic growth potential. The estimated incidence of IUGR is approximately 5–7% [1] and despite advances in obstetric care it represents a prevalent complication, related with short- and long-term morbidities [2].

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Recently, an active role of the placenta in the adaptation of fetal growth has been suggested. The placenta acts as a nutrient sensor [3] adapting its transport functions in response to changes of substrate supply and plays a key function in the regulation of fetal growth and programming [4].

The placental transport alterations observed in the IUGR are specific [3]; although the activity of some amino acids (taurine, leucine and cationic amino acids) transporters [5,6] in IUGR is reduced, other transport systems, like glucose transporters, remain unchanged. The severity of IUGR has been related with the most pronounced decreases in microvillous system A transporter activity, critical in mediating the uptake of glycine, serine and alanine across the syncytiotrophoblast maternal facing [7]. Placental changes in carnitine transfer in IUGR fetuses has not been documented, but modifications in placental carnitine transport in other pregnancy conditions like preeclampsia were suggested [8].

These previous data suggest that changes in the activity of some transporters are part of the cause of IUGR, whereas others are part of a feto–placental response to reduced fetal growth [3].

The role of carnitine in fetal–placental growth is under increasing interest. Fetal carnitine is derived from the mother via transplacental transfer. The high-affinity carnitine transporter OCTN2, expressed in placenta [9,10], is thought to be involved in the placental transfer of carnitine, but it has also suggested a low carnitine biosynthetic activity in the fetal–placental unit [11].

Neonatal carnitine values at birth can be influenced by maternal levels, as observed, for example, in preeclampsia [8].

LC is considered as a conditionally essential nutrient for newborns, especially premature ones, due to their reduced ability to synthesize it. The major portion of placental carnitine transfer occurs during the third trimester, so the tissue carnitine stored in preterm newborns are lower than in a term infants. Furthermore, breastfeeding or oral formula-feeding provide LC, but this nutrient is absent in most of the parenteral formulations used in preterm newborns. Therefore, the risk of carnitine deficiency in very-low-birth weight (VLBW) preterm infants is high, especially in pathological situations in which the start of enteral nutrition is delayed.

Small-for-gestational-age (SGA) babies could also represent a special risk group for carnitine deficiency as suggested by its low ability in fatty acid oxidation [12]. Nutritional recommendations in preterm newborns are based on accretion rates of specific fetal nutrients over the third trimester and they are not modulated by additional needs in sick preterm infants. Postnatal administration of carnitine increases plasmatic concentrations of carnitine and could improve lipid tolerance [13].

The initial interest by the nutritional effects of FC supplementation [14–16] and its repercussion in fatty acid metabolism has been branching out with the investigation of its potential effects on neonatal morbidity. Recent publications support a multi-factorial role of acylcarnitines in neuroprotection [17,18] and a possible relationship between carnitine and prevalent neonatal morbidities.

On the other hand, current knowledge of evolutionary changes of acylcarnitine profile in premature newborns is limited [19–25].

Universal nutritional supplementation in newborns is not recommended [26], even though it is a common practice in many neonatal units [27]. Our work, unlike the previous ones, is based on the investigation of a possible higher carnitine deficiency in IUGR preterm neonates. Demonstration of this deficit may contribute to establish high-risk subgroups of preterm newborns, who may benefit from a postnatal supplement with LC.

Patients and methods

Patients

Inclusion criteria

The study was carried out for a period of 6 years on VLBW preterm newborns (birth weight less than 1500 g) recruited from NICU of Complexo Clínico Universitario of Santiago de Compostela (Spain) by their first 2 d of life.

The authors selected this study population in order to ensure a period of parenteral nutrition in most of the patients. Trophic enteral feeding was usually started in the first 24–48 h of life. The increased rate of enteral volume was determined by the clinical situation of the patient. None of them received postnatal carnitine supplementation.

The participants were classified in two groups: appropriate-for-gestational-age (AGA) or SGA for their gestational age, defined those as newborns with birth weight lower than percentile 3 for their gestational age according to the Spanish birth percentiles published by Carrascosa et al. [28].

Exclusion criteria

Exclusion criteria included any VLBW preterm newborns with perinatal hypoxia-ischemia, inborn errors of metabolism, intraventricular hemorrhage grade III or IV, or advanced stages of kidney or liver disease or who need for hemofiltration or peritoneal dialysis.

Methods

A retrospective study was conducted over a 6-year period to evaluate the longitudinal profile of FC, total carnitine (TC) and acylcarnitines in both groups of preterm infants.

The aim of our study was to test the hypothesis that SGA preterm newborns represent a special risk group for carnitine deficiency. The carnitine deficiency marker used was the accepted FC/TC ratio (normal value: 0.7–0.95).

We defined carnitine deficiency as FC value lower than 40 μmol/L and FC/TC value lower than 0.7.

As a secondary outcome, we defined assessment of longitudinal differences of TC, FC and acylcarnitines between the two groups of study.

Total acylcarnitines (tAC) were measured by adding short-chain, medium-chain and long-chain acylcanitines. TC was obtained by adding FC and tAC.

Sample collection

The blood spots samples obtained for expanded neonatal screening (NBS) were used for the research, under ethical committee approval. In our region (Galicia, Spain), the expanded NBS includes two samples in preterm newborns: the first on the third day, after 48 h of milk intake, and the second on the 15th day. In some VLBW infants, where oral feeding was delayed, the date of the first sampling was delayed until the 5th day.

In some patients, two additional samples, i.e. on the 30th day and the 40th day of life, were available.

Tandem mass spectrometry

FC and acylcarnitines study was performed by tandem mass spectrometry with triple quadrupole equipment ESI-MS/MS API 2000 (Applied Biosystems Sciex, Toronto, Canada). The methodology used was developed by Millington et al. [29]. Acylcarnitines extraction was made using methanol with stable isotope-labeled patterns to allow the concentration calculation. The samples prepared were derivatizated with butanol in acid medium to increase the selectivity of the technique and finally measurements were performed by experiment precursor *m/z* 120 to 280 amu. The list of acylcarnitines studied include *short-chain acylcarnitines*:

acetyl- (C2), propionyl- (C·), butyryl- (C4), isovaleryl- (C5) and tiglyl-carnitine (C5:1*); medium-chain acylcarnitines*: hexanoyl- (C6), octanoyl- (C8), octenoyl- (C8:1), decanoyl- (C10), decenoyl- (C10:1) and dodecanoyl-carnitine (C12); *long-chain acylcarnitines*: tetradecanoyl-(C14), myristoleyl-c (C14:1), palmitoyl-c (C16), octadecanoyl-c (C18), oleyl-c (C18:1), hydroxymyristoyl-c (C14OH), hydroxypalmitoyl-c (C16OH) and hydroxyoleyl-carnitine (C18:1OH).

Statistical analyses

Student *t*-test was performed for the analyses of independent variables. A p value < 0.05 was considered significant. SPSS for Windows (version 15.0®, Chicago, IL) statistical packages were used for analyses.

Results

Study population

A total of 144 preterm infants, 73 AGA and 71 SGA, were included in the study. All patients were VLBW and 16% of them were extremely low birth weight (birth weight less than 1000 g). Table 1 presents the demographic characteristics in study population. Both groups showed a homogeneous distribution by sex (73 males and 71 females) and anthropometric birth parameters. The only significant difference was the gestational age (29 weeks in AGA and 31 weeks in SGA). Mean birth weight was 1247 g in AGA group and 1192 g in SGA group.

A total of 263 samples were processed, 108 corresponding to those collected on the third to fifth day of life and 81 to those picked up on day 15.

Table 1. Demographic characteristics of study population.

	AGA	SGA	*p* value
Birth weight	1247 g ± 213	1192 g ± 219	0.13
Birth length	37.8 cm ± 2.79	37.8 cm ± 2.34	0.85
Birth head circumference	27.1 cm ± 1.89	27.1 cm ± 3.56	0.95
Gestational age (weeks)	29.1 ± 1.77	31.9 ± 1.89	<0.001

AGA, appropriate-for-gestational-age; SGA, small for gestational age; SD, standard deviation.
Data presented as mean ± S.D.

Seventy-nine percent of the premature infants enrolled received parenteral nutrition (54% of the SGA and 84% of the AGA). The duration of the parenteral was 4.3 d in the SGA (range: 3–26 d) and 10.6 d in AGA group (range: 2–45 d). Enteral feeding was started on average in the first day in SGA and in the second day in AGA. Thus, by day 15, 100% of SGA premature newborns and 75% of the AGA ones were full-fed.

The evolution of TC, FC, acylcarnitines and FC/TC ratio over the first 5 weeks of life in all infants is summarized in Table 2.

Primary outcome

Carnitine deficiency is observed in both study groups throughout the monitoring period. The maximum FC value obtained in AGA was 36.05 µmol/L by day 40 and in SGA was 32.24 µmol/L by 3th–5th d.

FC/TC ratio remains under 0.7 for the entire monitoring period in AGA and SGA. According to this ratio, the higher carnitine deficiency was observed by day 3–5 (FC/TC: 0.46 ± 0.1 in AGA and 0.47 ± 0.1 in SGA) and by day 15 (FC/TC: 0.49 ± 0.1 in AGA and 0.50 ± 0.1 in SGA) in both study group.

There was no significant difference in FC/TC ratio between the two study groups.

Whereas tAC/FC ratio had a fluctuating evolution in AGA group, a progressive decrease of this ratio is observed in the group of restricted birth weight.

Secondary outcome

Unlike expected, a comparatively higher value of TC, FC and tAC was found in SGA group during the first 2 weeks of life, with significant differences in the three parameters on the day 3–5 sample. From the evaluated parameters, the major difference on this sample corresponded to the tAC ($p < 0.001$). When comparing individual carnitine esters, a significant difference highlights in C2 and C8 on day 3–5.

Evaluated parameters (TC, FC and tAC) equate by day 30 of life in both groups and, subsequently the trend reverses, reaching higher values in AGA group.

The only acylcarnitine evaluated with a lower value in SGA group during the whole study period is C5, significantly in the two 1st weeks of life ($p < 0.05$).

Table 2. Longitudinal profile of total carnitine, free carnitine, short-, medium- and long-chain acylcarnitines and carnitine deficiency markers between AGA and SGA newborns in capillary sample (median ± DS) (µmol/L).

	First sample (day 3–5) (*n*:108)			Second sample (day 15) (*n*:81)			Third sample (day 30) (*n*: 57)			Fourth sample (day 40) (*n*:17)		
	AGA	SGA	*p* value	AGA	SGA	*p* value	AGA	SGA	*p* value	AGA	S GA	*p* value
TC	51.81 ± 22.9	63.43 ± 24.0	0.01	38.78 ± 20.3	45.98 ± 20.1	NS	47.92 ± 24.7	47.12 ± 22.8	NS	64.46 ± 39.3	55.16 ± 17.3	NS
FC	25.65 ± 16.0	32.24 ± 14.4	0.02	20.75 ± 11.2	23.46 ± 12.2	NS	24.86 ± 16.2	25.01 ± 13.6	NS	36.05 ± 19.5	30.37 ± 9.5	NS
tAC	26.65 ± 9.6	32.26 ± 12.2	<0.001	18.58 ± 10.6	22.52 ± 10.0	NS	23.05 ± 13.0	22.11 ± 12.2	NS	28.41 ± 20.9	24.79 ± 11.0	NS
tACs	20.73 ± 8.6	25.65 ± 11.2	0.01	15.23 ± 9.0	18.38 ± 8.6	NS	20.24 ± 12.	18.84 ± 11.6	NS	24.43 ± 19.9	21.47 ± 10.2	NS
tACm	0.59 ± 0.2	0.61 ± 0.2	NS	0.52 ± 0.1	0.59 ± 0.1	NS	0.48 ± 0.1	0.54 ± 0.2	NS	0.54 ± 0.2	0.60 ± 0.1	NS
tACl	5.32 ± 1.8	5.56 ± 2.2	NS	3.22 ± 1.8	3.54 ± 2.0	NS	2.32 ± 0.9	2.71 ± 1.1	NS	3.43 ± 1.9	2.70 ± 1.0	NS
tAC/FC	1.27 ± 0.5	1.21 ± 0.5	NS	1.07 ± 0.5	1.07 ± 0.4	NS	2.32 ± 7.4	0.99 ± 0.4	NS	0.73 ± 0.2	0.88 ± 0.5	NS
FC/TC	0.46 ± 0.1	0.47 ± 0.1	NS	0.49 ± 0.1	0.50 ± 0.1	NS	0.50 ± 0.1	0.52 ± 0.1	NS	0.58 ± 0.0	0.56 ± 0.1	NS

Statistically significant difference at $p \leq 0.05$; NS: p value not significant.
TC, total carnitine (TC = free carnitine + total acylcarnitines); FC, free carnitine; tAC, total acylcarnitines; AGA, appropriate-for-gestational-age; SGA, small for gestational age; tACs, total short-chain acylcarnitines; tACm, total medium-chain acylcarnitines; tACl, total long-chain acylcarnitines.

In both study groups, a decline in TC, FC and tAC was documented at 15 d of life, with a larger reduction in SGA group. Afterwards there was a recovery, reaching values in the 5th week that outweigh initial ones in the SGA group.

Discussion

The current knowledge of carnitine and acylcarnitines profile in preterm infants is limited [19–25]. Moreover, acylcarnitines comparison with previous works is difficult because results differ according to the sample used, whole blood or plasma, with significantly higher results obtained in blood, due to the presence of a relatively high concentration of long-chain acylcarnitines in the erythrocyte membrane.

Although a carnitine deficiency has been suggested in SGA newborns, only two studies [22,23] have previously evaluated FC profile in IUGR. Akisu et al. study [22] showed differences in FC levels in full-term IUGR newborns compared with AGA ones, but not in premature IUGR infants. The second work [23] studied carnitine and acylcarnitine in newborns, sub-classified in AGA and SGA and according to gestational age. Their results demonstrated a carnitine deficiency in all neonates, with a greater deficit in IUGR newborns (defining those patients as newborns with birth weight less than 2500 g) and in those of 28–32 weeks of gestational age.

The terms intrauterine growth retardation (IUGR) and SGA are related, but not synonymous and this may be a confounding factor in the comparison of studies on this topic. IUGR refers to a process that causes a reduction in an expected pattern of fetal growth and SGA refers to an infant with birth weight lower than a predetermined cut-off value. In our study, we classified SGAs as those newborns with birth weight less than percentile 3 for their gestational age.

To the best of our knowledge , differences in acylcarnitine profile in VLBW infants, according to whether birth weight restriction exists, have not been previously evaluated. The novelty of our work lies in the comparative study between AGA and SGA VLBW preterm infants to determine whether SGA ones have an increased risk of carnitine deficiency.

A FC/TC value less than 0.70 is considered indicative of carnitine deficiency. The values obtained in the current work indicate a carnitine deficit in both groups that persists throughout the study period with a progressive improvement over the same. Lower FC/TC values were previously [23] documented in the first week of life in SGA newborns (FC/TC medium 0.32; SD 0.19). No significant differences in carnitine deficiency markers were found between the two groups.

The values of TC, FC and tAC in the present study were comparatively higher in SGA group over the two 1st weeks of life, with statistically significant differences in the three parameters between the two groups on day 3–5. The only acylcarnitine evaluated with a lower value in SGA group during the whole study period is C5, significantly in the first two samples (3th–5th day and 15th d).

Longitudinal evaluation showed a decrease, in both groups, in the values of FC, TC, tAC and short-, medium- and long-chain acylcarnitines on day 15, compared with the first sample obtained on day 3–5. These findings are in accordance with previous studies [19,25,30]. This documented decrease at 15 d in FC, TC and tAC was also observed in the Meyburg et al. study [19] in preterm infants of 22 to 27 weeks of gestational age, however in the group of 28–32 weeks this decline occurred before 7 d of age.

The obtained values of FC, TC and tAC equate on day 30, and subsequently the trend reverses, reaching higher TC, FC and tAC values in AGA group.

Since the period of primary parenteral feeding was the first 10–15 d of life in premature newborns, the decrease determined in the second sample (day 15) may be due to a lack of exogenous carnitine support, and the subsequent recovery in carnitine levels, which could reflect the progressive increase of carnitine intake linked to the rise of enteral feeding. In our population by day 15, 100% of the SGA and 75% of the AGA preterm infants studied, were full-fed.

The higher need of parenteral nutrition in AGA is congruent with their greater immaturity.

In the current study, the decrease in the three parameters determined on day 15 is greater in SGA group.

The plasma carnitine concentrations obtained after enteral and parenteral carnitine supplementation do not differ, thereby suggesting that enteral carnitine is well absorbed [14]. The enteral route in VLBW infants has the limitation that oral feeding during their first days of life is frequently delayed, with the exception of trophic supply, especially in those with concomitant serious illness like respiratory distress syndrome, sepsis or ductus arteriosus. For this population, the introduction of carnitine in parenteral solutions could represent an improvement in clinical care.

The aim of our work was to evaluate whether SGA preterm newborns could have a higher risk for carnitine deficiency and be candidates for carnitine supplementation. Our results indicate a carnitine deficiency not only in SGA newborns but also in AGA ones, throughout the study period. We consider that these findings reinforce the recommendation of carnitine supplementation in the population of VLWB infants, objective of our study.

Although the present study has limitations, its retrospective nature and the lack of data from cord blood, based on the results obtained, a carnitine deficiency was observed in VLBW preterm newborns during their first 5 weeks of life. In accordance, these infants must be carefully evaluated to ensure that their lipid metabolism is unimpaired. Although SGA premature infants could represent a subgroup of patients with increased risk of postnatal carnitine deficit, we did not find significant differences between AGA and SGA in FC/TC ratio during postnatal period. Further studies would be required to deepen the understanding of carnitine status in VLWB neonates.

Declaration of interest

The authors report no declarations of interest.

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