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Acquired carnitine abnormalities in critically ill children

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Abstract In order to characterize the role of carnitine during metabolic stress, we prospectively determined carnitine profiles in plasma and urine on admission, days 2, 5, 10 and 15, among 28 critically ill children free of any known conditions associated with secondary carnitine deficiency. More than 25% of plasma and 50% of urinary carnitine measurements were abnormal; 96% (27/28) of patients displayed on at least one occasion an abnormal [< -2 SD or $> +2$ SD] carnitine value in plasma. Three children had extremely low [< 10 μmol/l] free carnitine (FC) levels in plasma. Plasma esterified and FC levels on admission were not related to the risk of mortality [PRISM score], to muscle lysis [CK values], and to the caloric intake. Levels of FC and esterified carnitine in plasma were unrelated to those measured in urine.

Conclusion Abnormal plasma and urine carnitine measurements are frequently found in critically ill children; the biological significance of these perturbations remains unclear. Caution must be exercised before concluding that an abnormal carnitine value is indicative of an underlying hereditary metabolic disorder in this population.

Key words Carnitine · Child · Head injury · Heart defects · Sepsis

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Abbreviations *CK* creatine kinase · *CoA* coenzyme A · *CoASH* reduced coenzyme A · *EC* esterified carnitine · *FC* free carnitine · *ICU* intensive care unit · *PRISM* paediatric risk of mortality · *TC* total carnitine

Introduction

Carnitine (3-hydroxy-4-N-trimethyl-aminobutyrate) can be biosynthesized from its endogenous precursors lysine and methionine or exogenously derived from nutritional intake [27]. Carnitine allows the transfer of long-chain fatty acids from the cytoplasm to the mitochondrial matrix where their β-oxidation occurs, with resultant energy production [27]. Carnitine also regulates the intramitochondrial acyl to free coenzyme A (CoA) ratio [27]. Several mitochondrial pathways produce acyl CoA. Under conditions of metabolic stress, such as inborn errors of metabolism, diabetic ketoacidosis or hypoxia, there is an excessive production of acyl CoA, which is further transesterified by carnitine to regenerate free CoA [27]. In models of ischaemic reperfusion injury, the accumulation of acyl CoA esters has been shown to increase lipid peroxidation and to induce irreversible plasma membrane damage [13]. Consequently, carnitine may be of major importance in maintaining mitochondrial functions and cellular viability in critically ill patients [27].

Carnitine deficiency may result from excessive acyl CoA production coupled with increased urinary losses, insufficient carnitine intake or decreased endogenous biosynthesis. Critical illnesses may be associated with some of these processes. Increased urinary carnitine losses have been found in adult patients with acute hypercatabolic conditions such as the postoperative phase [35], burns [7], sepsis [17, 36], and trauma [10, 20]. There are no data on plasma or urinary carnitine levels in critically ill children. Recognition of carnitine deficiency in these patients may have both diagnostic and therapeutic implications. Indeed, abnormal plasma carnitine values may arise secondary to the acquired critical

illness but may also be the result of an undiagnosed inborn error of metabolism. L-Carnitine supplementation could be considered in children in hypermetabolic state or with myocardial dysfunction since carnitine may have positive inotropic effects [5], L-Carnitine supplements have also been shown to increase myocardial performance in children with cardiomyopathy associated with primary systemic carnitine deficiency and in patients with diphtheritic myocarditis [27]; it may also improve haemodynamic parameters in adults with cardiogenic or septic shock [16].

The goals of the present study were to determine plasma carnitine concentrations in critically ill children free of any known underlying metabolic disorder and to test whether the observed abnormalities were related to the risk of mortality or could be explained by muscle lysis, insufficient caloric intake and/or urinary carnitine losses.

Materials and methods

Population characteristics

From 1 August, 1991 to 1 May, 1992, we conducted a prospective study of 28 acutely ill children admitted to the paediatric intensive care unit (ICU) at Sainte-Justine Hospital with sepsis, severe head trauma or following cardiac surgery. All patients were aged 1–18 years, except for cardiac surgery cases who were considered eligible even if they were younger than 1 year of age. Sepsis was defined as clinical evidence of infection with all of the following criteria: (1) rectal temperature > 38°C; (2) sustained tachycardia (heart rate > 90th percentile for age and sex [9], present for more than 6 h after admission); (3) capillary refill time > 3 s; (4) positive blood culture within 48 h of paediatric ICU admission. Head trauma was considered severe if the Glasgow Coma Score was < 10 for at least 6 h after admission. The cardiac surgery group included children admitted to the ICU after an arterial switch, a Fontan procedure, repair of a complete endocardial cushion defect or repair of coarctation of the aorta. We excluded patients with the following comorbid states known to be associated with secondary carnitine deficiency [18, 27]: (1) inborn errors of metabolism; (2) Reye-like syndrome [14]; (3) use of valproic acid; (4) prior renal dysfunction (serum creatinine > 1.2 x upper limit of normal in the previous month); (5) prior hepatic dysfunction (ALT or AST > 2 x upper limit of normal in the previous month); (6) diabetes mellitus; (7) malnutrition (weight <10th percentile for age and sex [11]), and tricipital skinfold thickness <10th percentile for age and sex [30]; (8) use of parenteral nutrition at any time prior to paediatric ICU admission.

Data

The risk of mortality was assessed daily with the Paediatric Risk of Mortality (PRISM) score [25]. Weight was measured within 12 h of admission on a metabolic balance (Scale-Tronix 2001, 1978, White Plains, N.Y). Tricipital skinfold thickness measurements were obtained on admission in all patients, with a Lange skinfold caliper (HB 859-1-2, Cambridge Scientific Industries, 1985, Cambridge, Maryland), using the technique described by Tanner and whitehouse [34]. The mean of three consecutive measurements was compared to normal values established by Sempé et al. [30]. For each patient, daily energy intake from intravenous fluids, enteral and parenteral nutrition was established as follows: 4.0 kcal/g of dextrose (16.8 kJ), 4.0 kcal/g of amino acid (16.8 kJ) and 9.0 kcal/g of lipid (37.8 kJ). The study ended following 15 days of ICU stay or upon death or discharge from the paediatric ICU. Serial blood samples and 24-h urine collection (8 a.m. to 8 a.m.) were obtained upon admission to the paediatric ICU (day 0) and then on days 2, 5, 10 and 15. Three millilitres of heparinized blood was obtained via arterial cannula and was centrifuged at 5°C, 2200 rpm for 10 min. Blood and urine samples were kept frozen at −80°C until analysis. Internal validity was maximized by analysing simultaneously all samples from each patient. Plasma total carnitine and free carnitine concentrations were determined by radio-enzymatic assay using the method of McGarry and Foster [23] with the following modification: the binder for the reduced coenzyme A (CoASH) group, tetrathionate, was replaced by N-ethylmaleimide [24]. Esterified carnitine (EC) was calculated by substracting free carnitine (FC) value from total carnitine (TC). Urinary TC and FC were determined according to the method of Cederblad et al. [6]. Plasma creatine kinase (CK) levels were measured by spectrophotometry using a commercial kit (Diagnostics Chemicals Limited, 1992, Charlottetown, Prince Edward Island).

Definitions

Low plasma carnitine was defined as a value < -2 SD.

Statistical methods

Descriptive statistics are expressed as median and range. Z scores were calculated for plasma TC, FC, EC concentrations and EC/FC to ratio since normal values vary according to age [28]. Z scores were calculated according to reference values established in our laboratory from among 151 fasted children who were sampled before undergoing an elective surgical procedure. Pearson coefficients were established from a correlation matrix comprising Z scores of plasma carnitine values (EC and FC) on admission and the PRISM scores, the CK values and the caloric intake. Finally, plasma EC and FC values were each correlated with those measured in urine. The power to detect a relationship ($r = 0.6$) between these variables was 80%.

Ethics

For each patient, informed consent was obtained from the parents. The study was approved by the Ethics Committee of Sainte-Justine Hospital.

Results

Among the 28 children who entered the study, 9 had sepsis, 8 had severe head trauma and 11 had undergone cardiac surgery. There were 18 males (66%) and 10 females (34%). The median age was 65 months, with a range of 0.1–211 months. The median PRISM score on the day of admission to paediatric ICU was 16, with a range of 6–51; Three children with sepsis, two with trauma, and one cardiac surgery patient died in the paediatric ICU, leading to a 22% (6/28) mortality rate. During their ICU stay, 9 patients received intravenous parenteral nutrition and 9 were fed with a soy-based formula (Isocal).

Abnormal carnitine values were found among patients in all diagnostic categories and data were pooled for statistical analyses. Table 1 shows plasma carnitine concentrations over time and their respective Z scores. Abnormal results were observed for all plasma carnitine

Table 1 Plasma values and their respective Z scores for TC, FC, and EC values, and EC/FC ratio

Day	N[a]	TC		FC		EC		EC/FC	
		median	(range)	median	(range)	median	(range)	median	(range)
Values[b]									
0	28	61	(35–141)	24	(6–108)	34	(13–74)	1.3	(0.3–2.8)
2	22	63	(37–106)	31	(6–86)	25	(13–57)	1.1	(0.2–2.8)
5	13	58	(34–100)	30	(0.7–67)	27	(15–47)	0.9	(0.2–47)
10	8	75	(48–118)	53	(21–90)	25	(13–45)	0.5	(0.2–1.3)
15	5	88	(34–126)	52	(14–74)	28	(14–61)	0.7	(0.4–1.4)
Z scores[c]									
0	28	1.1	(−3.4–10.5)	−0.3	(−4.1–10.7)	1.6	(−2.8–6.6)	1.1	(−2.4–13.5)
2	22	0.1	(−3.0–6.9)	0.1	(−2.9–7.5)	0.3	(−2.2–4.4)	0.4	(−2.5–7.9)
5	13	0.5	(−2.4–6.1)	−0.4	(−2.8–4.8)	0.5	(−2.5–3.3)	0.3	(−2.5–149)
10	8	1.9	(−0.1–9.1)	2.6	(−0.5–7.9)	−0.6	(−2.2–2.4)	−1.7	(−2.6–0.9)
15	5	3.3	(−1.4–10.4)	2.5	(−1.3–5.7)	0.3	(−2.0–4.9)	−0.4	(−1.5–1.3)

[a] N, number of patients available for testing
[b] Values expressed in μmol/l
[c] Normal range: −2 SD to +2 SD

parameters: TC, FC, and EC concentrations, and EC/FC ratio. Table 2 provides data from three individual patients with plasma FC values lower than 10 μmol/l; values below this cutoff point are usually considered to be very low at any age. The proportion and percentage of abnormal plasma carnitine values on day 0 and at exit from the study are presented in Table 3. At the end of the study, abnormally elevated TC and EC levels, and EC/FC ratio were frequently found. However, only 4 children still showed low carnitine levels: a 15-year-old male admitted for trauma (FC = 20 μmol/l, TC = 46 μmol/l, EC = 26 μmol/l); a 12-year-old female admitted for trauma (FC = 20 μmol/l, TC = 71 μmol/l, EC = 51 μmol/l); a 12-year-old female admitted for cardiac surgery (FC = 14 μmol/L, TC = 47 μmol/l, EC = 33 μmol/l) and one 15-year-old female who had sepsis (FC = 20 μmol/l, TC = 57 μmol/l, EC = 37 μmol/l). All children survived, except for the second patient who developed brain death.

Table 2 Data from three children with severely decreased FC values (*M* male, *T* trauma, *S* sgosis, *CS* cardiac surgery)

	Patients		
	1	2	3
Sex	M	M	M
Age (years)	7	0.01	0.12
Diagnosis	T	CS	CS
Survival	yes	yes	yes
FC and EC on day 0[a]	6.1:29.8	14.6:18.5	12.4:34.5
FC and EC on day 2	34.8:28.4	8.7:20.9	6.3:40.6
FC and EC on day 5	25.5:22.9	31.4:27.3	0.7:33.1
FC and EC on day 10		50.0:18.5	21.2:26.8
FC and EC on day 15			14.1:19.4

[a] FC and EC are expressed in μmol/l

We used the PRISM score as a clinimetric index of the risk of mortality [25]. We measured plasma CK levels to assess muscle cell death [32]. Muscle lysis may increase plasma carnitine levels, as over 90% of the total body store of carnitine is within the intracellular compartment of striated muscle [27]. Table 4 shows that severity of illness peaked on the day of admission to paediatric ICU and that muscle lysis occurred from admission to day 2 in most patients. Statistical analysis revealed that Z scores of plasma EC and those of plasma FC on admission were not related to the PRISM scores, the CK levels or the caloric intake. As shown in Table 4, the energy intake of these patients was very low up to 5 days after paediatric ICU admission.

Table 5 shows the urinary excretion of carnitine over time. The proportion and percentage of abnormal uri-

Table 3 Proportion and percentage (%) of abnormal results for plasma TC, FC, EC, and EC/FC ratio

	TC		FC		EC		EC/FC	
All samples	35/76	(46)	33/76	(43)	25/76	(32)	24/76	(31)
On admission (day 0)								
Abnormal results[a]	15/28	(53)	10/28	(36)	11/28	(39)	10/28	(36)
results > +2 SD	11/28	(39)	5/28	(18)	9/28	(32)	9/28	(32)
results < −2 SD	4/28	(14)	5/28	(18)	2/28	(7)	1/28	(4)
At exit from the study[b]								
Abnormal results[a]	12/22	(55)	14/22	(63)	11/22	(50)	11/22	(50)
results > +2 SD	11/22	(50)	10/22	(45)	8/22	(36)	8/22	(36)
results < −2 SD	1/22	(5)	4/22	(18)	3/22	(14)	3/22	(14)

[a] Normal range: −2 SD to +2 SD
[b] Includes only 22 patients for whom more than one sample were available

Table 4 PRISM score, plasma CK values and patients' energy intake

Day	N[a]	PRISM score		CK[b] (U/l)		Energy intake[c] (cal/kg/day)	
		median	(range)	median	(range)	median	(range)
0	28	16	(6–51)	309	(8–705)	7.6	(0.8–29.1)
2	22	7	(0–22)	226	(17–512)	1.5	(0.02–36.7)
5	13	8	(4–18)	90	(8–411)	8.4	(0.8–47.6)
10	8	10	(2–17)	42	(10–464)	43.5	(7.8–60.0)
15	5	4	(0–9)	32	(14–79)	32.6	(19.6–44.5)

[a] *N* number of patients available for testing
[b] Normal range: 20–184 U/l
[c] 1 kcal = 4.2 kJ

Table 5 Urinary concentration of TC, FC, EC, and EC/FC ratio

Day	N[a]	TC[b]		FC[b]		EC [b]		EC/FC	
		median	(range)	median	(range)	median	(range)	median	(range)
0	11	27.2	(9.8–40.5)	10.0	(3.5–32.5)	9.8	(3.7–23.8)	1.0	(0.2–6.7)
2	11	11.8	(5.7–28.6)	3.8	(1.4–10.8)	6.9	(3.1–22.6)	1.4	(0.4–8.7)
5	10	15.1	(5.8–30.7)	9.8	(1.5–22.2)	7.7	(4.2–18.4)	1.2	(0.3–3.3)
10	7	18.5	(10.3–37.3)	8.5	(1.7–20.9)	12.3	(2.7–27.4)	0.9	(0.3–7.1)
15	4	24.0	(9.0–85.9)	13.3	(5.1–54.8)	10.7	(3.9–31.1)	0.8	(0.6–0.8)
Normal			2.8–13.8		1.3–4.8		1.5–9.0		1.0–2.9

[a] *N* number of patients available for testing
[b] TC, FC and EC are expressed in μmol/nmol creatinine

nary carnitine values among patients in whom a complete urine collection was available are presented in Table 6. Both FC and EC excretion were increased throughout the study period. Statistical analysis showed that plasma FC and EC levels were not related to urinary concentrations of FC or EC.

Discussion

We studied prospectively plasma and urinary carnitine concentrations in critically ill children. Although the plasma carnitine level is an imperfect indicator of the total body carnitine pool [36], decreased plasma levels have often been shown to be related to low tissue concentrations [1, 26, 27]. We may have slightly underestimated the plasma carnitine levels by drawing blood samples from an arterial line, given the previous report of a venous to arterial differential of 3–4 μmol/l [29]. Despite these limits, serial assessments of plasma carnitine may provide a reliable estimate of the cellular content of carnitine.

As in inborn errors of metabolism, elevated plasma values of EC in critically ill children suggest an increased production of CoA esters of organic acids with an increased mitochondrial workload. Carnitine insufficiency, characterized by low FC levels associated with an increased EC/FC ratio, may permit the accumulation of toxic products and lead to inefficiency of mitochondrial metabolic pathways requiring free CoASH. We found abnormal plasma values of TC, FC and EC, and of EC/FC ratio amongst all but one patient, on at least one

Table 6 Proportion and percentage (%) of abnormal urinary concentrations of TC, FC, EC, and EC/FC ratio

	TC		FC		EC		EC/FC	
All samples	24/43	(56)	20/43	(47)	31/43	(72)	31/43	(72)
On admission (day 0)[a]								
Abnormal results[b]	8/11	(73)	9/11	(82)	6/11	(55)	6/11	(55)
results > normal	8/11	(73)	9/11	(82)	6/11	(55)	1/11	(10)
results < normal	0/11	(0)	0/11	(0)	0/11	(0)	5/11	(45)
At exit of the study								
Abnormal results[b]	16/21	(76)	17/21	(81)	11/21	(52)	18/21	(85)
results > normal	16/21	(76)	17/21	(81)	11/21	(52)	3/21	(14)
results < normal	0/21	(0)	0/21	(0)	0/21	(0)	15/21	(71)

[a] Includes only 11 patients in whom a complete 24-h urine collection was available
[b] Normal range: TC, 2.8–13.8 mmol/mmol creatinine; FC, 1.3–4.8 mmol/mmol creatinine; EC, 1.5–9.0 mmol/mmol creatinine; EC/FC, 1.0:2.9

occasion during the study period. However, the magnitude of these abnormalities was variable, as reflected by the wide ranges in the Z scores for carnitine values. This may be explained by the small number of patients studied, by the heterogeneity of both the intensity and the nature of the stress to which these children were submitted, and by variations in individual metabolic responses. In most critically ill children, carnitine abnormalities resolved spontaneously as only 4 patients maintained low FC levels and increased EC/FC ratio at exit from the study despite the absence of intake of carnitine. This suggests that endogenous carnitine biosynthesis is usually sufficient to maintain or re-establish homeostasis during the first 2 weeks following paediatric ICU admission.

Three patients (11%) displayed a plasma FC level lower than 10 μmol/l. Such depressed FC values are commonly thought to indicate an underlying inborn error of metabolism. It seems very unlikely that these three subjects were afflicted with any inherited metabolic disease considering the low frequency of these disorders and our stringent selection criteria, aimed at excluding patients with inborn errors of metabolism. Therefore, our results suggest that caution should be used in the interpretation of carnitine measurements in a paediatric ICU setting. Before undergoing extensive evaluation for a possible inborn error of metabolism associated with secondary carnitine deficiency, carnitine measurements should be repeated several weeks after the acute phase of illness.

Increased plasma EC levels can be found in conditions associated with renal failure [8], intravascular haemolysis [3], polymorphonuclear and mononuclear cell destruction [21]. During sepsis [12] and major burns [2], Demirkol et al. have reported a dynamic shift in carnitine concentration from plasma and erythrocytes to leucocytes which may be secondary to enhanced energy metabolism of white blood cells. However, in this study, plasma carnitine levels correlated poorly with the PRISM score; a more accurate physiologic assessment of oxygen debt through either direct measurements of oxygen consumption or gastric tonometry may provide more reliable indicators of the physiologic stress of critically ill patients [15, 22, 31].

About 98% of total body carnitine content is stored within skeletal muscle [27]. In adults with trauma or sepsis, Iapachino et al. [20] reported a direct relationship between the urinary excretion of TC or FC and the severity of hypercatabolism as measured by nitrogen balance and urinary output of 3-methylhistidine. We found no relationship between plasma CK and carnitine values, suggesting that muscle lysis per se did not contribute significantly to abnormal plasma carnitine values.

Fasting can increase EC, EC/FC ratio through the formation hydroxybutyrate and acyl CoA [4]. In our sample severe illness precluded significant energy intake for up to 5 days following admission to paediatric ICU. Although all patients received intravenous dextrose, the exact amount necessary to suppress ketogenesis in critically ill children is unknown. We failed to demonstrate any relationship between plasma carnitine and the caloric intake. The measurement of ketone bodies levels during these conditions may establish to what extent fasting per se accounts for the observed abnormalities.

Plasma carnitine concentrations are subject to regulation by the kidneys [19]. Carnitine is highly conserved in humans: at normal physiological concentrations in plasma, more than 90% of filtered carnitine is reabsorbed by the kidney [27]. Increased urinary excretion of carnitine was found frequently in our patients. These high urinary carnitine losses seemed to be equally attributable to FC and EC, as indicated by a median EC/FC ratio in urine close to 1. In adult patients with protein-energy malnutrition, sepsis, liver or renal dysfunctions, Wennberg et al. [36] found a lower FC/TC in urine than in plasma or muscle and suggested that FC renal reabsorption was higher than that of EC. On the contrary, Iapachino et al. [20] reported that increased urinary carnitine losses were mainly attributable to elevated FC excretion in adults with trauma and sepsis. Moreover, direct inhibition of FC transport in the kidney due to the accumulation of acylcarnitines has been reported in states of secondary carnitine deficiency due to acyl CoA oxidation disorders [33]. Thus, in critically ill children, wasting of carnitine in the urine may occur through both massive urinary excretion of EC in combination with a decreased FC renal threshold. However, we must be cautious in our interpretation; it is difficult to make any inferences concerning the renal handling of carnitine in critically ill patients since their renal function is rarely at a steady state. Interestingly, we observed that urinary losses of FC occurred despite the presence of decreased FC levels in plasma. We have been unable to detect any relationship between FC and EC concentrations in plasma and urine.

In conclusion, our results suggest that critically ill children are prone to carnitine abnormalities as manifested by decreased plasma FC and increased EC/FC ratio. It is unknown if these perturbations are related to the involvement of carnitine in the processes of metabolic detoxification in conditions of severe acute illness associated with excessive acyl CoA production. It should be determined if carnitine abnormalities are related to markers of cellular dysoxia commonly used such as oxygen derived haemodynamic parameters or gastric tonometry. Specific analysis of the different types of acyl carnitine accumulating during acute severe illnesses may help to determine if distinct metabolic pathways become inefficient during these episodes. More data are needed to determine if carnitine abnormalities have any detrimental consequences such as reduced cardiac function or cellular membrane peroxidation.

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