Acta Paediatrica Hungarica, 27 (2), pp. 107—113 (1986)

Influence of protein intake and liver function on acid base balance in premature infants

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In 43 patients with late metabolic acidosis (LMA) the factors promoting LMA were investigated. Postnatal adaptation was disturbed in all cases, in 35 patients acidosis developed after introduction of formula feeding. Whereas no differences were observed in renal function (urine volume and renal molar excretion) between acidotic and non-acidotic patients, there was a significantly higher concentration of bile acids in serum (26.1 $\pm$ 9.6 *vs* 98.6 $\pm$ 21.6 μmol/l), a significantly increased fractional volume of stools (8.2 $\pm$ 1.3 *vs* 11.4 $\pm$ 1.9% of intake, and higher faecal fat excretion (26.5 $\pm$ 5.2 *vs* 39.1 $\pm$ 6.6% of faecal weight) in LMA patients than non-acidotic formula-fed infants.

It is suggested that impaired postnatal development of liver function caused by severe disturbances of postnatal adaptation (respiratory distress, persistent fetal circulation, sepsis) is one of the most important factors in the pathogenesis of LMA. Thus, liver function should be checked before a protein intake surpassing that of a breastfed infant is introduced. Concentration of the serum bile acid level seems a reliable marker of LMA.

Since its first description, late metabolic acidosis (LMA) is considered a result of a temporary disproportion of renal H^+ elimination capacity and dietary intake of nonvolatile acids [16–20, 22, 25]. As a rule, LMA can be observed during formula feeding, especially if the protein intake is high [29]. In spite of this, only Schwartz et al [25] estimated the renal elimination capacity during LMA but they failed to find significant differences between acidotic and non-acidotic infants.

The metabolic response to formula feeding is characterized above all by a loading of liver function. The higher protein intake during formula feeding results in hyperaminoacidaemia and increased amino acid losses as well as in nonphysiologic cholestasis [7, 26]. It was therefore attempted to estimate the influence of postanatal development of liver function on the occurrence of LMA in premature infants appropriate for gestational age (AGA).

Patients

All admitted AGA premature infants who developed LMA between 1st of February, 1980, and 31st of August, 1984, were subjected to study. A total of 8 patients developed LMA during human milk (HM) feeding (Group 1), and in 35 patients LMA occurred on changing HM to formula (Group 2). To compare these patients, Group 3 included AGA premature infants without any perinatal problem fed

TABLE I

Data of infants studied (M ± SD)

	Patients with late metabolic acidosis		Controls	
	Fed human milk (Group 1)	Fed formula (Group 2)	Fed human milk (Group 3)	Fed formula (Group 4)
Gestational age, weeks	30.3 ± 1.8	30.9 ± 1.8	31.3 ± 1.6	32.9 ± 1.9
Weigth at birth, g	1413 ± 299	1798 ± 328	2072 ± 391	1812 ± 359
Length at birth, cm	40.6 ± 1.9	42.7 ± 2.2	44.7 ± 2.6	42.9 ± 2.3
Postnatale age, days	25.3 ± 4.9	20.8 ± 6.2	21.0	29.4 ± 4.9
Number	35	8	54	11

native HM from the first day of life and studied on the 21st day of life, and in patients of Group 4 nutrition had been changed from HM to formula (1.7 g protein/100 ml) during the third week of life without developing LMA. The data of the studied infants are summarized in Table I.

METHODS

The diagnosis of LMA presupposed a poor weight gain and a base excess of more than −5 mmol/l after the 7th day of life. At the same time, cardiac decompensation as well as bacterial infectious diseases had to be excluded. In all patients the clinical course including postnatal adaptation, development of body weight, and the concentration of bilirubin in serum on the 3rd day of life were determined. In selected patients of Groups 2, 3 and 4 we estimated in addition the

amount of urine and faeces;

fat excretion in stools gravimetrically by chloromethanol extraction;

osmolality of urine;

renal total and alpha-amino-nitrogen excretion by Kjeldahl and ninhydrin method;

serum concentration of alpha-amino-nitrogen and bile acids by the method of Senger et al [26].

For statistical analysis Student's *t*-test was applied.

RESULTS

As compared to the corresponding control group, patients with LMA were characterized by severe complications during the first days of life (Table II) which caused the significantly ($p < 0.01$) longer time of total parenteral nutrition as shown in Table III. The maximum postnatal weight loss was significantly ($p < < 0.05$) higher and the birthweight was reached later ($p < 0.01$) in both LMA groups than in the corresponding control groups (Table III). On the 3rd day of life the serum bilirubin concentration was significantly ($p < < 0.01$) elevated in LMA patients compared to patients without LMA (Table III).

Comparison of patients suffering from LMA during HM feeding with those fed formula (Tables II, III), the groups with HM feeding was characterized by a lower gestational age, lower birthweight, a higher incidence of severe disturbances of postnatal adaptation, a longer time of total parenteral nutrition, and a lower base excess.

TABLE II

Clinical findings

	Patients with late metabolic acidosis		Controls	
	Fed human milk Group 1	Fed formula Group 2	Fed human milk Group 3	Fed formula Group 4
Apgar-score below 4	1	13	0	0
Apgar-score 4 to 7	0	9	9	3
Respiratory distress syndrome	3	3	0	1
Sepsis	3	4	0	0
Persistent fetal circulation	1	5	0	1
None	0	2	45	6
Number	8	35	54	11

TABLE III

Cumulative protein intake and protein intake on days LMA, duration of postnatal total parenteral nutrition (TPN), weight gain, and serum bilirubin level on the 3rd day of life and acid–base balance on the day of LMA (M ± SD)

	Patients with ate metabolic acidosis		Controls	
	Fed human milk Group 1	Fed formula Group 2	Fed human milk Group 3	Fed formula Group 4
Protein intake:				
cumulative (g/kg/d)	1.97 ± 0.36	2.05 ± 0.39	1.98 ± 0.38*	2.09 ± 0.41**
Day of LMA (g/kg/d)	2.32 ± 0.40	3.98 ± 0.47	2.31 ± 0.41*	3.81 ± 0.51**
Duration of TPN (days)	6.2 ± 2.9	3.1 ± 1.9	7.1 ± 2.8 (hours)	1.9 ± 1.9
Postnatal weight loss (per cent birthweight)	7.1 ± 3.1	6.8 ± 2.6	4.2 ± 2.5	5.4 ± 2.9
Day reaching birth-weight	22.6 ± 6.8	19.7 ± 6.6	8.2 ± 4.2	10.3 ± 5.1
Serum bilirubin level (μmol/l)	248.6 ±23.9	217.9 ±49.6	154.0 ±49.3	181.4 ±48.2
pH	7.31 ± 0.028	7.29 ± 0.034	7.36 ± 0.031*	7.34 ± 0.039**
Base excess (mmol/l)	−7.6 ± 1.2	−8.8 ± 1.1	−1.1 ± 1.2*	−2.9 ± 1.3**

* referred to the 21th day of life
** referred to the 1st day of formula nutrition

Urine volume decreased during the change from HM to formula feeding ($p < 0.01$), but there was no difference between LMA patients and patients without LMA (Fig 1). Renal molar excretion as well as renal nitrogen losses were significantly higher ($p < 0.01$) in formula fed patients than in infants fed HM (Fig 2), but there was no differences between acidotic and non-acidotic patients.

Whereas no differences in renal molar excretion could be observed between patients fed formula with

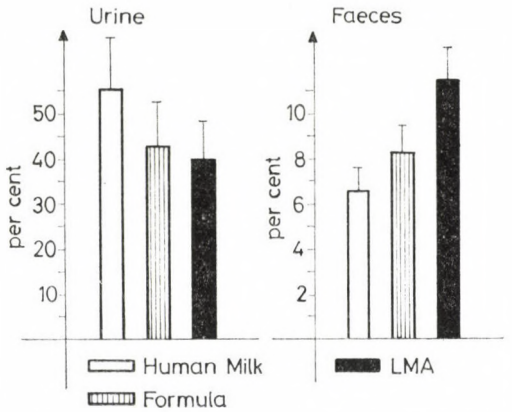

FIG. 1. Volume (M $\pm$ SD) of urine and stools are percentage of intake in patients fed human milk (Group 3), in patients without acidosis after change from human milk to formula (Group 4), and in patients fed formula with late metabolic acidosis (Group 2)

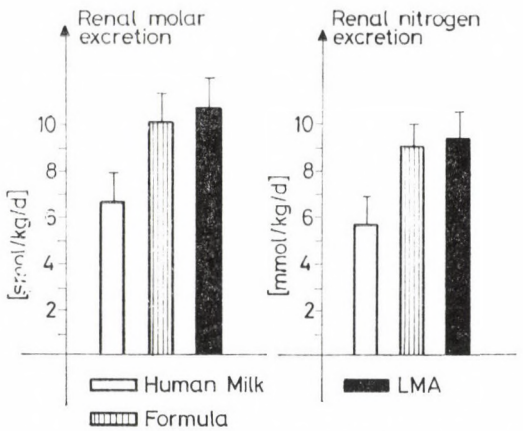

FIG. 2. Daily renal nitrogen and molar excretion (M $\pm$ SD) in patients fed human milk (Group 3), in patients after change from human milk to formula without acidosis (Group 4), and in patients fed formula with late metabolic acidosis (Group 2)

(Group 2) and without (Group 4) LMA, there were significant differences ($p < 0.05$) in faecal volume, as shown in Figure 1. The faecal excretion of fat was lowest in Group 3 ($18.1 \pm 3.4\%$ of stool weight) and highest in Group 2 ($39.1 \pm 6.6\%$ of stool weight). In Group 4, fat excretion was more than in the group fed HM but less than in the formula fed LMA group ($26.5 \pm 5.2\%$ of stool weight).

During formula feeding, the serum alpha-amino-nitrogen concentration increased significantly as compared to Group 3 ($p < 0.01$), but there were no differences between formula fed acidotic and non-acidotic patients. In

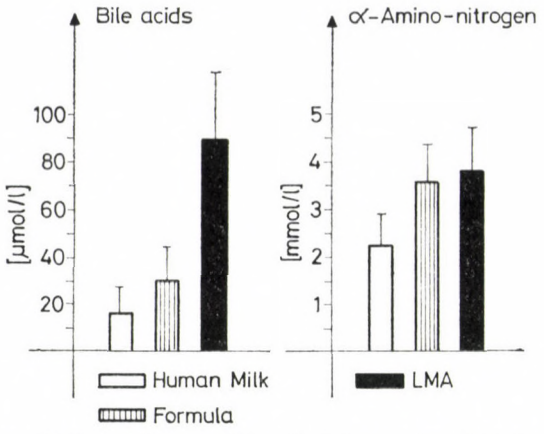

FIG. 3. Concentrations of bile acids (µmol/l) and alpha-amino-nitrogen (mmol/l) in serum (M ± SD) in patients fed human milk (Group 3), in patients after change from human milk to formula without acidosis (Group 4), and in patients fed formula with late metabolic acidosis (Group 2)

contrast, the serum bile acid concentration was significantly different ($p < 0.01$) between acidotic and non-acidotic formula fed patients (Fig 3).

DISCUSSION

LMA is usually described to result from an insufficient renal function related to dietary non-volatile acids [16–20, 22, 25], but the present results seem to confirm the data of Schwartz et al [25] showing that renal function in LMA patients is in the range normal for both gestational and postnatal age [1, 6, 9, 16]. In contrast, the limited liver function seems to be a more important factor in these patients: elevated serum bile acid levels, higher volume of stools and increased faecal fat excretion may be a result of an aggravated neonatal cholestasis. The results of Blitzer et al [4] showing an influence of high amino acid concentrations in the extracellular space on hepatocellular bile acid uptake may explain these findings.

It is remarkable that in all patients with LMA, postnatal adaptation was disturbed. This may lead to liver dysfunction in different ways, as follows.

Hypoxia of hepatocytes changes the cellular metabolic situation by decreasing protein synthesis as a basic condition of postnatal development [15]. As a clinical consequence of such disturbances, it is well-known that total parenteral nutrition leads to hepatocellular dysfunction and not only during the first days of life [3, 5, 14, 21] and, in addition, to an insufficient stimulation of gut hormones which are important factors in postnatal development of the gastrointestinal tract [2, 14]. Bacterial toxins may also have a role in the disturbed development of liver function [8]. Thus, damage of hepatocytes may explain the finding that the same elevation of serum amino acids in both

formula fed groups resulted in a significantly higher increase of serum bile acid concentration in the LMA group (Fig 3) and that during HM feeding the development of LMA is based on a disturbance of liver function. The same was observed by Svenningsen and Lindquist [29] while other authors presumed that in newborns LMA had no connection with postnatal disturbances [16–18, 20, 22].

The observed effects of non-human protein on bile acid metabolism cannot directly explain the acid-base disturbance. The decreased digestion of food may lead to excretion of bases and this may be related to LMA.

Despite the high interest in problems of newborn nutrition, publications related to LMA are scarce. Some investigators demonstrated metabolic acidosis during formula feeding without description of LMA as a disease entity [17, 24]. On the other hand, the absence of LMA is regarded as a sign of good quality nutrition [10, 11, 27, 28]. From the present data it seems that the acid-base balance reflects the quality of nutrition as well as the postnatal development of liver function. It is concluded that for low birthweight infants a protein intake of more than 2.5 g/kg/day should be prescribed only with a good liver function. The serum concentration of bile acids seems to be a good marker to estimate the metabolic situation of the liver. Concentrations of more than 40 μmol/l are signs of cholestasis, and the substitution of HM for formulas containing more protein than that of HM cannot be recommended.

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Received March 27, 1985

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