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Urinary tract infection presenting with conjugated bilirubinaemia and the plasma amino acid pattern in young infants

by

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Fasting blood glucose and plasma free amino acid levels were determined in 16 infants (average postnatal age, 44 ± 6 days) suffering from urinary tract infection associated with jaundice and cholestasis. There were no significant differences in the fasting blood glucose values of the control and jaundiced babies. The concentration of two glucogenic amino acids; alanine and lysine, decreased significantly and phenylalanine, citrulline and cystine levels were elevated, suggesting an impairment of the metabolism of these amino acids in the liver. A close positive correlation was found between bilirubin, SGPT and phenylalanine levels, suggesting a relationship between hepatic damage and the measured phenylalanine concentration. After two to four weeks of antibiotic treatment the urine became sterile bilirubinaemia disappeared and the amino acid levels returned to normal.

The most common condition associated with cholestatic jaundice in young infants is urinary tract infection rather than congenital atresia of the biliary ducts or neonatal hepatitis. The usual clinical picture is of a young infant who is failing to thrive, lethargic or irritable, and suffering from fever, jaundice, and moderate hepatomegaly [15]. Hepatocellular impairment is the main factor in the production of jaundice [2].

The major role of the liver in glucose and amino acid homeostasis has long been recognized. A serious impairment of hepatic glycogen synthesis and gluconeogenesis frequently leading to fasting hypoglycaemia has been reported in acute viral hepatitis [4]. No information is available concerning these biochemical functions in liver injury associated with urinary tract infection in young infants.

The question has been investigated by measuring fasting blood glucose and individual plasma free amino acid concentrations in such infants.

Material and Methods

Sixteen infants ranging in age from 6 to 80 days and admitted over a two year period were included in the study.

The clinical data are presented in Table I. Most babies were prematurely born, only three infants had a gestational

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age of >35 weeks. Jaundice was evident in all cases; both conjugated and unconjugated bilirubin concentrations were elevated in their plasma. The former bilirubin fraction comprised 56% of the total bilirubin level which varied from 1.6 to 25.2 mg/dl. The observed bilirubinaemia was moderate in the majority of cases. Plasma bilirubin concentration was below 2 mg/dl in 4 cases, between 2 and 5 mg/dl in 6, between 5 and 10 mg/dl in 4 cases and only two infants (both septic cases) had plasma bilirubin levels higher than 10 mg/dl. SGOT values were elevated in 8, SGPT values in 4 cases. Both SGOT and SGPT were above normal (12 IU) in 3 infants. All of the 16 infants had at least two to three urine cultures with 10^4 or more Gram negative organisms per cu. mm. Most infants were infected with E. coli, but all had sterile blood cultures. Blood urea nitrogen level was determined in 6 cases and ranged from 12 to 29 mg/dl. There were no reducing sugars in the urine and serological tests for Australia antigen, rubella, cytomegalovirus and toxoplasmosis were negative. Intravenous pyelograms and cystourethrograms were performed in half of the patients and 4 out of the 8 showed some kind of abnormality (Table I).

After 2 to 4 weeks antibiotic treatment the urine culture became sterile and both

TABLE I

Clinical data of infants with jaundice

Sex	Gest. age, wks	B. weight, g	Postnatal age, days	B. weight at examination, g	Total Bilirubin mg/dl	Conjugated Bilirubin mg/dl
M	—	1110	70	2500	2.7	1.3
M	30	1480	60	2800	2.5	1.3
F	27	1400	80	3400	1.6	0.4
F	30	1430	42	1950	2.4	1.4
M	—	1200	67	2600	2.2	1.7
F	31	1320	77	2500	3.1	2.0
F	38	3160	21	2700	9.3	7.1
F	28	1310	36	1400	7.2	4.3
M	33	2460	5	2300	25.2	6.4
M	33	2240	17	1900	5.1	3.0
F	38	3450	42	4200	14.0	11.7
M	32	1470	32	1500	7.1	5.3
F	—	1700	40	2000	1.6	1.5
M	37	2900	23	2700	3.5	1.7
M	36	1630	60	2000	1.8	1.2
F	—	1700	39	2100	1.8	1.0

fractions of bilirubin decreased gradually. Liver biopsy was performed in 6 cases at the time of peak bilirubin levels.

Histology showed a non-specific reactive hepatitis with cholestasis and some infiltration of the portal tracts with inflammatory cells.

Fasting blood glucose and plasma amino acid levels were determined from 1.0 ml of blood taken at 0900 hr. A control group of 49 premature infants with similar gestational age, birth weight, postnatal age and actual bodyweight were selected who were admitted to the unit over the same two years period when feeding regimen (formula- feeding) and care were practically the same (Table II).

Blood glucose was estimated by the o-toluidine method (4) and the plasma level of 17 individual amino acids by automated ion-exchange chromatography using Beckman Multichrom 4225 analyser. Amino acid analyses were made at the same time in both groups. Specimens of venous blood collected in heparinized tubes were promptly centrifuged and the plasma was deproteinized by addition of four volumes of 5% sulphosalicylic acid. Protein-free supernatant was immediately frozen and stored at −20°C until assayed.

For statistical analysis Student's *t*-test was used and regression equations were calculated by the method of least squares (paired analysis).

and urinary tract infection

UN, mg/dl	Fasting blood glucose, mg/dl	SGOT (IU)	SGPT (IU)	Urine culture	Liver biopsy*
—	97	10	3	E. coli 10^4	+
—	—	16	10	E. coli 10^5	+
—	56	29	15	E. coli 10^4 10^5	+
29	71	21	7	E. coli and Klebsiella 10^5	+
—	—	—	—	E. coli 10^4	+
—	—	—	—	E. coli 10^6	—
—	59	14	5	E. coli 10^5	+
—	—	42	23	E. coli 10^4	+
—	50	10	2	E. coli 10^5	—
—	83	12	8	E. coli 10^4	—
40	—	12	14	E. coli 10^5	—
12	45	62	43	E. coli 10^4	—
14	62	3	2	Klebsiella and Proteus 10^5	—
—	87	16	3	E. coli 10^5	—
14	—	25	7	E. coli 10^6	—
19	51	8	3	E. coli 10^5	—

* Nonspecific reactive hepatitis with cholestasis (see text).

TABLE II

Control and jaundiced infants
(M + SE)

	Control	Jaundice with urinary tract infection	Significance
Gestational age, weeks	33 ± 1	33 ± 2	NS
Birth weight, g	1742 ± 75	1873 ± 174	NS
Postnatal age, day	35 ± 3	44 ± 6	NS
Body weight at examination, g	2184 ± 58	2409 ± 175	NS
Mean fasting blood glucose, mg/dl	67 ± 2	67 ± 6	NS
BUN, mg/dl	10 ± 1	21 ± 5	< 0.001
n	49	16	

RESULTS

Mean fasting blood glucose concentrations were the same in the control and study groups (Table III). The mean blood urea level was significantly ($p < 0.001$) higher in the jaundiced infants, but urea levels were available for not more than 6 cases and among them only two babies showed levels markedly exceeding the upper limit of the normal (6—20 mg/dl) range.

Total and individual fasting plasma free amino acid levels are shown in Table III and Figure 1. The mean total concentrations of 17 amino acids were very similar in the two groups. Alanine and lysine levels were significantly lower, and plasma phenylalanine, cystine and citrulline were significantly higher, in the study group. Plasma tyrosine concentrations were also higher in the jaundiced group but the difference did not reach the level of significance.

Total and conjugated bilirubin levels were related to the plasma concentration of each amino acid found to be significantly lower or higher as compared to controls. A significant linear correlation was found only between total and direct reacting bilirubin levels and plasma phenylalanine concentrations (Figure 2), and there was a positive linear correlation between SGPT and plasma phenylalanine levels ($r = 0.7$, $p < < 0.05$).

The relationship between serial bilirubin and phenylalanine levels in the period of antibacterial treatment in 6 infants are shown in Figure 3. Plasma phenylalanine gradually decreased parallel with the fall of conjugated bilirubin concentration in most cases. There was no relationship between plasma phenylalanine levels and postnatal age in the control group, so a decline in plasma phenylalanine was considered a sign of improving liver function. By the time of recovery from

TABLE III

Plasma free amino acid levels in normal controls and infants with jaundice and urinary tract infection (M ± SE) (μmol/l)

	Control	Urinary tract infection and jaundice	Significance
Taurine	75 ± 18	79 ± 14	NS
Aspartate	47 ± 4	50 ± 4	NS
Citrulline	19 ± 3	45 ± 7	< 0.05
Proline	280 ± 32	248 ± 52	NS
Glycine	258 ± 17	228 ± 14	NS
Alanine	367 ± 20	261 ± 20	< 0.01
Cystine	48 ± 9	87 ± 10	< 0.01
Valine	193 ± 14	188 ± 20	NS
Methionine	28 ± 2	29 ± 4	NS
Isoleucine	60 ± 5	50 ± 6	NS
Leucine	111 ± 8	98 ± 9	NS
Tyrosine	129 ± 14	164 ± 50	NS
Phenylalanine	163 ± 22	277 ± 72	< 0.05
Lysine	251 ± 34	124 ± 11	< 0.05
Ornithine	93 ± 9	83 ± 10	NS
Histidine	73 ± 11	95 ± 10	NS
Arginine	76 ± 6	59 ± 5	NS
Total	2271 ± 30	2165 ± 118	NS
n	39	16	

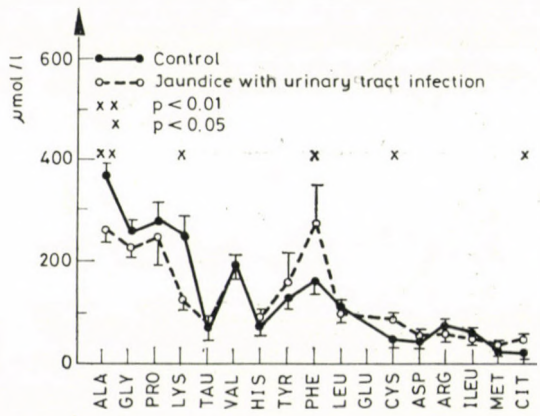

FIG. 1. Plasma aminogram in jaundice associated with urinary tract infection (M ± SE)

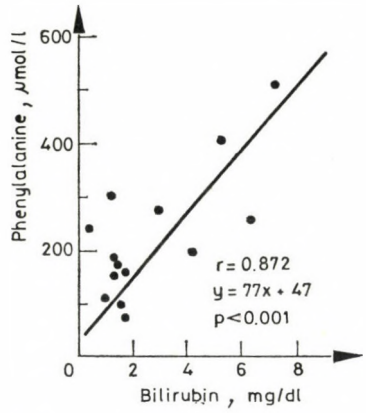

FIG. 2. Plasma conjugated bilirubin and phenylalanine levels in jaundice associated with urinary tract infection

the urinary tract infection, the rest of the amino acids also returned to normal.

The molar ratio of $\left(\frac{\text{Val}+\text{Ileu}+\text{Leu}}{\text{Tyr}+\text{Phe}}\right)$ suggested as a liver function test [16] has been calculated and is shown in Figure 4. The ratio was approximately 1.5 in the controls and was reduced to 0.92 in the study group ($p < 0.01$). The lower value of the quotient was mainly due to the higher level of aromatic amino acids included in the numerator, the plasma concentration of the branched chain amino acids remained normal.

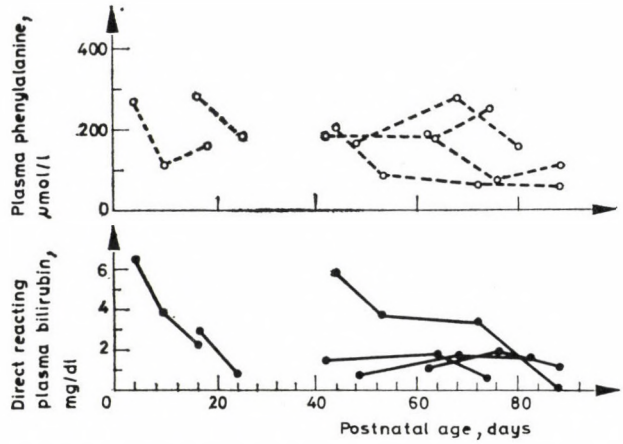

FIG. 3. Serial bilirubin and phenylalanine levels in 6 jaundiced infants with urinary tract infection

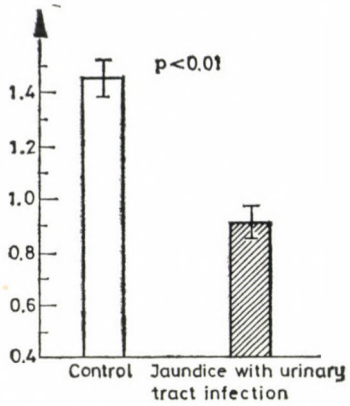

FIG. 4. $\frac{\text{Val} + \text{Ileu} + \text{Leu}}{\text{Tyr} + \text{Phe}}$ molar ratio in jaundice associated with urinary tract infection

DISCUSSION

Urinary tract infection in early infancy is frequently associated with jaundice [15]. It has been suggested that jaundice develops in these infants as a result of haemolysis [17] and toxic hepatitis [2] with intracellular and intracanalicular bile stasis. Except for the mild bilirubinaemia, the usual liver function tests are normal in this condition. Abnormal histology, on the other hand, is highly suggestive of liver impairment.

Blood glucose homeostasis, as far as it can be judged from the normal fasting blood glucose values, is maintained, but there are considerable distortions in the fasting plasma levels of some amino acids. Thus, the levels of alanine and lysine, two important glucose precursors, were reduced by 30 and 50%, respectively (Table III and Figure 1).

Since fasting blood glucose levels remained normal and no correlation was found between the degree of bilirubinaemia and the level of any of these two amino acids, it would be difficult to comment on the possible gluconeogenic significance of the hypoalaninaemia and hypolysinaemia [11].

It is a well established fact that tyrosine metabolism is abnormal in patients with liver disease. Fasting levels of tyrosine tended to be high in these patients [8]. Felig et al. [4] too found elevated fasting tyrosine levels in viral hepatitis. Recently, high tyrosine levels have been found in neonatal hepatitis [18] and in 4 preterm babies with mild cholestasis and rickets [6]. In the present study a small nonsignificant rise in tyrosine and a considerable and significant ($p < 0.05$) elevation in phenylalanine have been observed (Table III and Figure 1). Furthermore, there was a positive linear correlation between bilirubin and phenylalanine levels (Figure 2).

One must be careful when interpreting tyrosine and phenylalanine levels in young infants. Tyrosinaemia

and associated hyperphenylalaninaemia due to transient adaptive impairment of catabolism is a common neonatal condition, particularly frequent in premature babies [17, 14]. On the other hand, the protein quantity and quality of food is a major determinant of the plasma level of aromatic amino acids in that age group [3, 13]. On the basis of these considerations, infants with comparable gestational and postnatal age, as well as body weight and feeding-regimen were selected as controls.

As compared to control babies, the observed hypertyrosinaemia and hyperphenylalaninaemia were moderately, but in the case of phenylalanine clearly abnormal and can be considered as a sensitive biochemical parameter of liver impairment. This assumption is strongly supported by the observation that plasma phenylalanine levels have gradually declined during antibiotic treatment in parallel with the falling bilirubin values (Figure 3).

In adults, Soeters and Fischer [16] found a close correlation between molar ratio of the branched chain amino acids and the aromatic amino acids and the severity of liver damage associated with hepatic encephalopathy. The mean ratio was approximately 3—3.5 in the normal human adult and 0.6—1.2 in those suffering from hepatitic encephalopathy. We were able to show a fall of this ratio in a like manner in urinary tract infection associated with jaundice and cholestasis. It was surprising to see that a slight and apparently reversible liver damage noted in our patients produced a ratio similar to that observed in severe liver impairment leading to hepatic encephalopathy. It should be stressed, however, that our normal control values were also much lower than in adults, so the reduction of the ratio, significant though it may be, was far less dramatic than in hepatic encephalopathy. It also has to be kept in mind, as Soeters and Fischer had pointed out [16], that the elevation of the ratio is not at all specific for liver disease and stimuli such as sepsis, diuresis, stress, and catecholamine discharge can lead to increased plasma aromatic amino acids and decreased branched chain amino acids.

We found no apparent explanation for the elevated citrulline level. The plasma concentrations of the other (dibasic) amino acids participating in the urea cycle remained normal.

Hypercystinaemia may also be a small though significant biochemical sign of liver impairment, possibly indicating a further delay in the maturation of the enzyme(s) of the transsulphuration pathway which is particularly immature in preterm babies [5].

As regards the significance of the present findings, it can be concluded that *(1)* the distortion of the plasma aminogram indicates a moderate and reversible liver damage caused by urinary tract infection in young infants; *(2)* although the hypertyrosinaemia and hyperphenylalaninaemia observed were of moderate degree in most cases, their untoward effect on the developing nervous system cannot be excluded [9, 10]. In the most severe

cases follow-up investigations seem to be justified to distinguish it from the potentially harmful hypertyrosine and hyperphenylalaninaemias commonly seen in premature infants.

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