

A Case of Carbamyl Phosphate Synthetase Deficiency

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ARASHIMA, S. and MATSUDA, I. *A Case of Carbamyl Phosphate Synthetase Deficiency.* Tohoku J. exp. Med., 1972, 107 (2), 143-147 — A case is reported of a 2-month-old female infant with carbamyl phosphate synthetase deficiency in whom persistent vomiting appeared 7 days after birth, with irregular eye movement. Failure to thrive, hypotonia and a generalized atrophy of the brain were observed. This is the fourth case of carbamyl phosphate synthetase deficiency in the literature. ——— carbamyl phosphate synthetase deficiency

Numerous reports on congenital hyperammonemia due to urea cycle enzyme deficiency are available. However only three cases with carbamyl phosphate synthetase deficiency and normal ornithine transcarbamylase were described. (Freeman *et al.* 1964, 1970, Hommes *et al.* 1969, Kirkman and Kiesel 1969) Recurrent vomiting, failure to thrive and mental retardation were commonly found in these cases but some differences in clinical findings exist among the cases: in the case of Hommes (1969) hyperglycinemia and ketosis were not found, and blood ammonia was found to be only slightly elevated.

A case of carbamyl phosphate synthetase deficiency is reported here.

CASE REPORT

A 2-month-old female, the only child of unrelated parents was referred to us because of persistent vomiting since 7 days after birth. The birth weight was 2.65 kg. No abnormalities were noted in the perinatal period. On admission weight was 2.5 kg (normal, 5.6 ± 0.6) and the body length was 53 cm (normal, 58.5 ± 2.4). The patient had irregular eye movement and hypotonia, but no convulsion was seen. The liver and spleen were not enlarged. Laboratory investigation revealed the following data: Hb 13.7 g/100 ml; erythrocyte $473 \times 10^4/\text{mm}^3$; leucocyte 7,400/ mm^3 . Serum electrolytes, pH and bicarbonate concentration were within a normal range. SGOT was 111 units, SGPT 50 units, alkaline phosphatase 47 Kind-King units, and fasting blood glucose 90 mg/100 ml. No sugar and no protein was found in the urine.

Pneumoencephalography revealed generalized atrophy of the brain (Fig. 1), but no abnormalities in EEG were observed. In radiological examination the gastro-intestinal tract was normal. The optic fundi were also normal.

Received for publication, November 1, 1971.

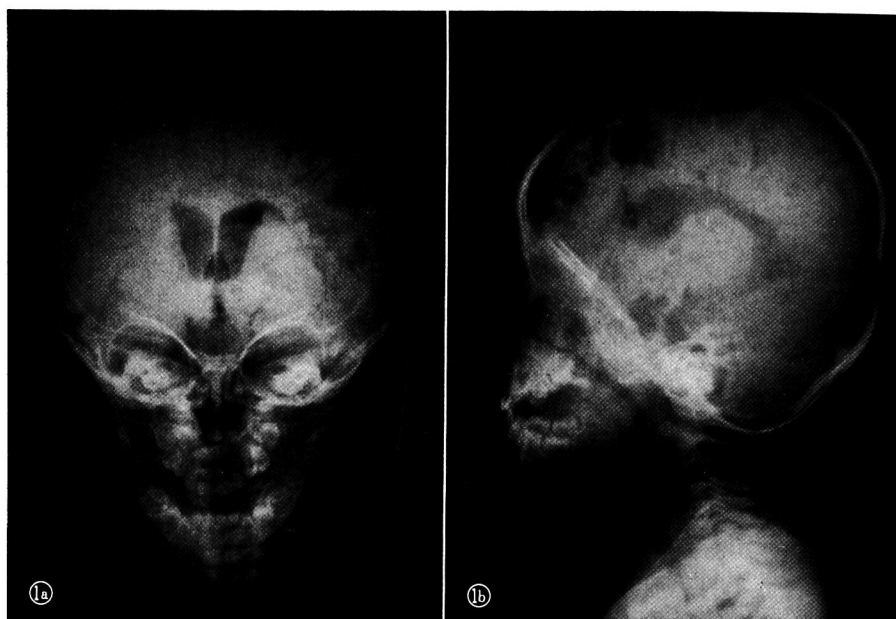


Fig. 1. Pneumoencephalography, showing generalized cortical atrophy.

During hospitalization the patient did not gain weight. After administration of low protein milk (1 g/kg of body weight), vomiting dramatically disappeared.

When the patient was put on a diet of food containing protein of lower than 2 g/kg/day, no vomiting was observed, although irregular eye movement showed no improvement. Under the suspicion of hyperammonemia, blood ammonia was measured by Seligson and Hirahara's method (1957), and it was found to be as high as 130 $\mu\text{g}/100\text{ ml}$ with protein intake 1.5 g/kg/day and 110 $\mu\text{g}/100\text{ ml}$ with protein intake 1.0 g/kg/day showing a slight elevation, while blood ammonia with ordinary protein supply amounted to 20–60 $\mu\text{g}/100\text{ ml}$ in normal infants.

Urea-N values were lower in plasma and amounted to 3–4.2 mg/100 ml with a protein intake 1.0–1.6 g/kg/day. For the treatment of the disease, we administered desiccated thyroid and orotic acid in association with low protein diet.

SPECIAL STUDIES

Serum and urine amino acids

Amino acid content in serum and urine was analyzed by the method of Stein and Moore (1954) using a Hitachi KLA type 3 amino acid analyzer. The results were within normal range.

Glucose tolerance test

After intravenous injection of glucose solution (1 g/kg body weight), blood sugar was measured every 5 minutes for half an hour. Glucose assimilation

constant (K) was graphically calculated. In the patient it was 4.3, indicating a moderate increase and, therefore, glucose utilization was deduced to be slightly reduced.

Urea cycle enzyme in the liver

The liver sample of the patient was obtained by surgical biopsy. Postmortem samples of other patients without liver disease within a few hours after death were used as controls. The activity of urea cycle was measured by the method of Brown and Cohen (1959). Necropsy sample of the control and material from

TABLE 1. *Liver enzymes of urea cycle*

	Patient	Control
Carbamyl phosphate synthetase	13.4	100,123
Ornithine transcarbamylase	6,080	6,850
Argininosuccinate synthetase	138	84
system		
Arginase	7,550	6,910

unit: $\mu\text{moles/g wet weight/hr}$.

patient were examined simultaneously. The results are listed in Table 1. As can be seen, carbamyl phosphate synthetase was 13.4 units, representing a fall to approximately 13% of the control. Other enzyme activities in the urea cycle were within a normal range.

DNA and RNA content in the liver

Liver DNA and RNA were extracted following the method of Schmidt and Thannhauser (1945) and were determined by ultraviolet absorption. The DNA and RNA concentration in the patient liver were 2.45 mg/g wet weight tissue (control 1.3 mg/g) and 4.6 mg/g (control 3.6 mg/g), respectively.

Histology of the liver

Histological findings of the patient's liver were normal.

Orotic acid in urine

The amount of urinary orotic acid measured by the method of Rogers and Porter (1968) was found to be almost undetectable in the patient, while 1.4–2.0 mg/day was obtained in the control.

COMMENT

Persistent vomiting from 7 days after birth, failure to thrive, irregular eye movement, hypotonia, generalized cerebral atrophy and slightly elevated blood ammonia suggested that the patient had an inborn error of the urea cycle metabolism. A diagnosis of carbamyl phosphate synthetase deficiency was confirmed by assay of the liver enzyme. As in the case of Hommes *et al.* (1969) in which blood ammonia was as high as 100 $\mu\text{g}/100\text{ ml}$, in the present case only a

slightly elevated blood ammonia may have been the result of a low protein intake as deduced from persistent vomiting and administration of low protein diet for the treatment. It seems to be difficult to conclude that Hommes *et al.*'s case (1969) did not originally have hyperammonemia, as no data concerning blood ammonia was available before the admission.

Urinary orotic acid excretion in the present case was found to be extremely lower than that of the control. And, as described in our previous report, urinary orotic acid in the patient with ornithine transcarbamylase deficiency was markedly elevated to 50.1 mg/day (Matsuda *et al.* 1971).

These results suggest that there is a common pool of carbamyl phosphate for urea formation and pyrimidine synthesis. Therefore it may be mentioned that pyrimidine synthesis might be disturbed by a reduced common pool of carbamyl phosphate due to a defect of carbamyl phosphate synthetase. Arakawa *et al.* (1969) gave aminopterin to newborn rats and demonstrated the disturbance of brain development through the inhibition of purine synthesis. A similar possibility, in addition to the ammonia intoxication, might be considered in the occurrence of the brain damage in the present case. Determination of hepatic DNA and RNA contents, however, gave normal results compared with the control. Since pyrimidine synthesis in brain is more prominent than in liver, our results do not rule out the above-mentioned possibility. In the observation of Hommes *et al.* (1969) another possibility of brain damage was suggested to be due to carbamyl phosphate synthetase deficiency in the brain tissue itself. They pointed out that the fall of the activity of this enzyme in the brain tissue was found when the patient died. But Brown and Cohen (1960) did not establish the presence of this enzyme in tissue other than liver and intestinal mucosa. Some doubt still remains with regard to this point.

In the hematopoietic mouse spleen, Tachibana and Ito (1967) found another carbamyl phosphate synthetase with different properties. This enzyme was reported to be inhibited by metabolic products of UTP (Tachibana and Ito, 1967). This appears to be carbamyl phosphate synthetase contributable to pyrimidine synthesis. But it is not clear whether this enzyme is present in human tissues.

Reduced blood sugar utilization was in agreement with Freeman's (1964, 1970) case and Hommes' (1969) case, but no hyperglycemia was found in fasting in our case.

In contrast to the Freeman *et al.*'s (1964, 1970) and Kirkman and Kiesel's (1969) observations, hyperglycinemia and ketosis were not found in our case as well as in that of Hommes *et al.* (1969). This discrepancy might be related to the protein intake, as was seen in the level of blood ammonia.

Basing on the fact that thyroid hormone stimulates the activity of carbamyl phosphate synthetase (Metzenberg 1961), desiccated thyroid might be given in association with a low protein diet. According to our hypothesis orotic acid administration should be recommended expecting normal pyrimidine synthesis in the brain.

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