

## Short reports

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### Severe neonatal citrullinaemia

Among the small number of cases of citrullinaemia so far described, the range of clinical severity is wide (Wick *et al.*, 1973; Scott-Emuakpor, Higgins, and Kohrman, 1972). The 5 acutely ill newborn babies so far described with this disease have all died despite energetic treatment (Wick *et al.*, 1973; Okken, Van der Blij, and Hommes, 1973). The patient described here was investigated from birth because 2 sibs had died of undiagnosed illness on the third day of life. Treatment started on the first day achieved survival and good developmental progress until the age of 7 months when delayed treatment of an acute infection caused fatal hyperammonaemia.

#### Methods

Venous blood was taken, usually 1 hour after the 8 a.m. feed, into a heparinized tube in ice. The blood ammonia was estimated using the Hyland Blood Ammonia Test. The upper limit of normal for adults and older children is 100  $\mu\text{g}/100\text{ ml}$  in this laboratory. Limited experience with newborn babies has suggested that levels up to 140  $\mu\text{g}/100\text{ ml}$  may be normal. Amino acids in urine and serum were studied by high-voltage electrophoresis (HVE) on paper (Tippett, Danks, and Dimech, 1972). Serum and urine amino acids were quantitatively determined by column chromatography on a Bio-Cal amino acid analyzer (Model BC-200) based on the method of Spackman, Stein, and Moore (1958). Serum and CSF were deproteinized using 3% sulphosalicylic acid.

#### Case report

A male was delivered by lower uterine segment caesarean section, performed because the fetal heart slowed during labour which had been induced at 39 weeks' gestation. Apgar score was 3 at birth, and 5 at 5 minutes of age. Endotracheal intubation and assisted respiration were employed and 20 minutes elapsed before normal spontaneous respiration was established.

The parents were born in the same small Italian town but knew of no consanguinity. Their first 2 babies (1 male, 1 female) had both died on the third day with progressive cerebral depression. There was a healthy 13-year-old son. The induction of labour was planned to improve the care of the baby in whom a metabolic illness was anticipated.

When transferred to the Royal Children's Hospital at 4 hours of age the baby was irritable with symmetrical,

jittery limb movements, but was otherwise healthy. Amino acid levels in cord blood were normal by HVE, but HVE of urine at 4 hours of age showed a slight increase in citrulline, which became more definite by 12 hours of age. Blood obtained 24 hours after birth showed an enormous increase in citrulline (808.8  $\mu\text{mol}/\text{l}$ , 14.2 mg/100 ml) and mild hyperammonaemia (154  $\mu\text{g}/100\text{ ml}$ ), confirming the suspicion that this baby suffered from citrullinaemia. Complete serum amino acid analysis is shown in the Table. By this time the

TABLE

*Serum amino acid concentrations ( $\mu\text{m}/\text{l}$ ) in a patient with citrullinaemia at 24 hours after birth*

Alanine	808.7
Arginine	Trace
Aspartic acid	54.0
Citrulline	808.8
Cystine	93.5
Glutamine*	Increased above normal levels
Glycine	599.3
Histidine	Trace
Isoleucine	68.2
Leucine	80.9
Lysine	358.9
Methionine	82.9
Phenylalanine	84.5
Proline	521.7
Serine	285.0
Threonine	366.0
Tyrosine	73.3
Valine	Trace

\*Glutamine and glutamic acid could not be quantitated due to the conversion of glutamine to glutamic acid.

jittery movements had become frankly convulsive. These were controlled with phenobarbitone.

Feeding had been restricted to 5% dextrose by mouth from 8 hours of age. Difficulty in achieving an intake of protein sufficient to allow growth without serious hyperammonaemia was anticipated. However, a protein intake of 1.0 g/kg was given in 8 3-hourly feeds (using SMA and later Enfamil\*) without undue rise in blood ammonia. Trials of human growth hormone (2.5 units daily) and of tri-iodothyronine (10  $\mu\text{g}$  daily) at two different levels of protein intake (1.0 g and 1.5 g) revealed no beneficial effect. A feed containing protein 1.7 g/kg was established (7 feeds per 24 hours).

On this regimen moderate growth (100 g weekly) was achieved and blood ammonia levels remained within the

\*SMA, Wyeth Ltd.; Enfamil, Mead Johnson.

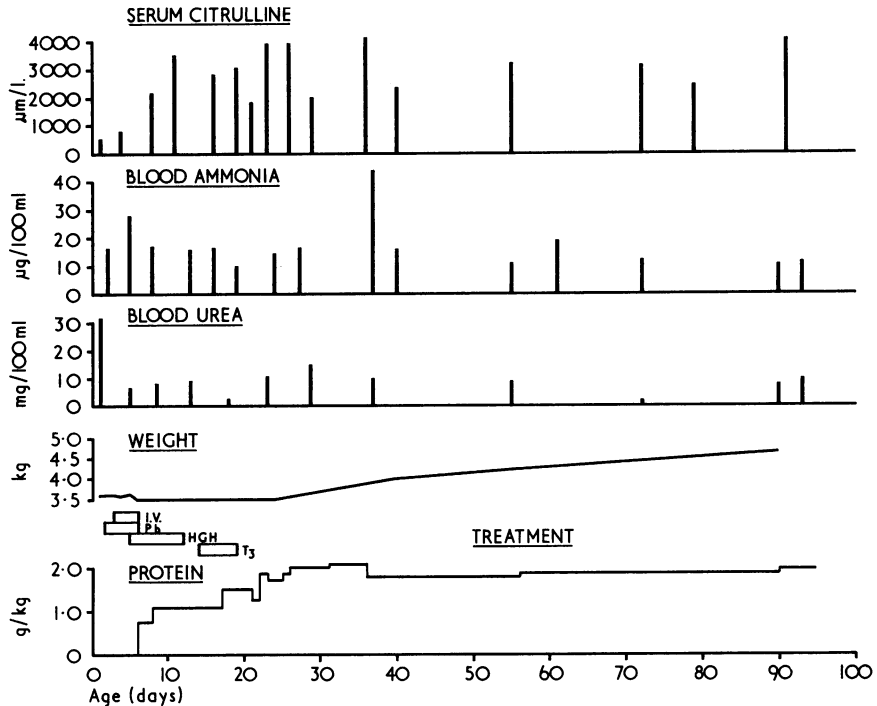


FIG.—Growth and changes in the blood levels of ammonia, urea, and citrulline with age, dietary protein intake, and hormone therapy. I.V., intravenous dextrose; Pb, phenobarbitone; HGH, human growth hormone 2.5 units daily; T<sub>3</sub>, tri-iodothyronine 10 μg daily.

range of 120 μg/100 ml to 180 μg (Fig.). Better growth seemed desirable and protein intake was increased to 2 g/kg at 4½ weeks of age. The blood ammonia level promptly rose to 450 μg/100 ml, and quickly dropped back to 180 μg when the protein intake was reduced to 1.7 g. At 3 months of age the blood ammonia level had fallen to 80 μg/100 ml and 2 g protein was tolerated. At 5 months of age, growth slowed and repeated episodes of mild hyperammonaemia occurred with teething. Hair growth was sparse and arginine deficiency was suspected. Arginine supplements (120 mg/kg) caused dramatic clinical improvement, weight gain, and growth of hair.

Throughout the whole period of observation the serum citrulline level remained very high, varying between 1253 μmol/l. to 3888 μmol/l. without any apparent relation to the protein intake. Blood urea was always below 15 mg/100 ml (Fig.).

The baby's jittery movements diminished rapidly after the first 2 or 3 days of life, and disappeared by 4 months of age. He smiled at 5 weeks. At 3 months of age he had very good head control, he followed people around him with obvious interest, and responded enthusiastically to his mother and his older brother. At 7 months he was sitting firmly and could reach out for toys without losing balance. He was able to roll to obtain toys.

At 7 months he developed an acute illness with fever

and vomiting. The severity of this episode was unfortunately underestimated by several doctors for 24 hours and he was deeply unconscious before effective intravenous fluid and glucose administration were started. Blood ammonia levels rose to 1500 μg/100 ml, and the use of exchange transfusions and of insulin failed to regain metabolic control. He died, and permission for a necropsy was refused.

### Discussion

This case is reported to point out that newborn infants with severe citrullinaemia can be treated successfully if protein restriction is instituted before symptoms develop and to emphasize that every episode of infection must be regarded as potentially life-threatening in babies with this disease.

The early deaths of this baby's 2 sibs suggested that he would also have died in the newborn period if he had not been diagnosed and treated, thus sharing the fate of all other reported cases of severe neonatal citrullinaemia (Wick *et al.*, 1973; Okken *et al.*, 1973). The normal intellectual development shown at 7 months of age indicated that he had survived without serious brain damage despite his

anoxic birth. His death during an acute infection could be interpreted as indicating that he was merely living on borrowed time and that a fatal catabolic illness was inevitable at some stage. However, we believe that the unfortunate delay in recognizing the severity of this episode and in starting effective treatment provides an adequate explanation. As emphasized by Wick *et al.* (1973), every intercurrent illness must be treated energetically; fluid and glucose sufficient to meet caloric requirements must be given by intravenous infusion if necessary.

Unfortunately, the opportunity for presymptomatic treatment of citrullinaemia arises only occasionally in new babies born into families in which previous cases have been diagnosed, and in rare families like the present one in which a new baby is investigated because of previous unexplained deaths (Danks, 1974).

Fluctuations in the clinical condition of this baby corresponded closely to the blood ammonia levels, supporting the idea that this is the noxious compound in citrullinaemia (Wick *et al.*, 1973). His ability to develop normally while serum citrulline levels were 100 times that of normal infants appears to contradict claims that citrulline itself is harmful (Okken *et al.*, 1973). Arginine supplements form an important part of the treatment, for arginine becomes an essential amino acid in these patients.

### Summary

Diagnosis of citrullinaemia was achieved at 36 hours in a baby whose 2 sibs had died in the newborn period without diagnosis. Control of blood ammonia levels by a low-protein diet allowed normal development until the age of 7 months, when delayed treatment of an acute infection allowed fatal hyperammonaemia to develop.

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## Maternal histidinaemia

Maternal histidinaemia was first reported in 1971 by Neville *et al.*, who described a 4-year-old boy whose 23-year-old mother had histidinaemia. The child appeared to be normal and of average mental development (IQ 107).

Our interest in this condition dates from 1969, when an expansion of the New Zealand phenylketonuria (PKU) neonate screening programme providing Guthrie Inhibition Assays (GIA) of blood phenylalanine, methionine, leucine, and tyrosine levels was extended to include a GIA for blood histidine. This resulted in the discovery of considerable numbers of transient elevations of neonatal blood histidine. At least one case of maternal PKU has been discovered by examining the mother of a newborn child with hyperphenylalaninaemia (Coffelt, 1964), and it has been a long-standing practice in our laboratory to request a dried blood spot from the mother of each child with hyperphenylalaninaemia. We instituted a similar procedure for mothers of children who had an initial GIA for histidine of 8 mg/100 ml or greater. From 1 January 1970 to 31 October 1973, 1556 such mothers were tested without the detection of a single case of maternal histidinaemia. However, in studying the relatives of a case of histidinaemia found in a mental hospital survey, we discovered a 37-year-old female sib with this condition. She had 5 children. Her family, and our study of it, are described here.

### Family study

In the course of a biochemical study of 1780 mentally retarded and psychiatric patients in two institutions in 1972, using blood GIAs and early morning urine specimens, a mentally retarded 27-year-old male with