tival fever by inoculating adenoviruses into the nose or throat, whereas swabbing them onto the conjunctiva leads to events closely paralleling the naturally occurring disease.² Furthermore, the efficacy of large and small particle aerosol spread of rhinovirus over a range of 70 cm is low in comparison with hand to hand contact.⁶ The cribs in the infants' house are farther apart than 70 cm and it seems unlikely that droplets propelled by coughing or sneezing could reach the conjunctival sac of an infant in an amount sufficient to produce infection.

The fact that three healthy adults were implicated in the spread of disease from one wing to another of the infants' house and also to two nurseries raises the possibility of hand to eye transmission. At night the children sleep at home where infants, who do not have intimate contact with one another during the day, have prolonged and close association with parents and siblings. Thus, a family containing both an infant and a toddler was probably a key link in the chain of infection. The three mothers who worked as nurses in the infants' house and in the first nursery affected could have transmitted the infection while bathing the children under their care or wiping away eye or nose secretions.

Finally, the fact that the outbreak was confined to infants and toddlers, aged 4 to 20 months, despite ample exposure through intimate household contact with older age groups, requires explanation. Earlier experience has shown that secondary family attack

rates for type 3 adenovirus decrease with age, which implies that adults and older children may have been infected previously with resultant prolonged immunity.² This could account for the limited spread of pharyngoconjunctival fever recorded here.

We thank Dr L Ranon of the Central Virus Laboratory, Ministry of Health, Israel, the nurses of Kibbutz Tirat Zvi, and C Wendel, for secretarial assistance.

References

- ¹ Baum SG. Adenovirus. In: Mandel GL, Douglas RG, Bennett KE, eds. *Principles and practice of infectious diseases*. New York: John Wiley & Sons, 1979:1353-61.
- ² Bell JA. Epidemiology of pharyngoconjunctival fever. *Am J Ophthalmol* 1957;43:36-40.
- ³ Fox JP, Hall CE, Cooney MK. The Seattle virus watch. VII. Observations of adenovirus infection. *Am J Epidemiol* 1977;105:362-86.
- ⁴ Germanis M, Jeansson S. Ocular illness in association with adenovirus type 3 infection. *Scand J Infect Dis* 1973;5:243-8.
- ⁵ Kendall EJC, Riddle RW, Tuck HA, Rodan KS, Andrews BE, McDonald JC. Pharyngo-conjunctival fever. School outbreaks in England during the summer of 1955 associated with adenovirus types 3, 7 and 14. *Br Med J* 1957;ii:129-36.
- ⁶ Gwaltney JM, Moskalski PB, Hendley JO. Hand-to-hand transmission of rhinovirus colds. *Ann Intern Med* 1978;88:463-7.

Correspondence to Dr J Herman, Kibbutz Tirat Zvi, Beth She'an Valley 10815, Israel.

Received 17 July 1984.

Successful treatment of severe carbamyl phosphate synthetase I deficiency

M VAN DE BOR, P MOOY, D VAN ZOEREN, R BERGER, H H VAN GELDEREN, AND H L TEIJEMA

Departments of Paediatrics, University Hospitals Leiden and Groningen, The Netherlands

SUMMARY We describe a girl with neonatal hyperammonaemia due to carbamyl phosphate synthetase I deficiency. Treatment consisted of protein restriction from the second day of life. Sodium benzoate was given for three weeks after birth and again from 7 months of age together with sodium phenylacetate to improve protein tolerance. Growth and development are normal at 15 months of age.

In carbamyl phosphate synthetase I deficiency the

urea cycle enzyme that converts ammonia to carbamyl phosphate is deficient, leading to hyperammonaemia. Patients with little or no enzyme activity (neonatal form) present with vomiting, lethargy, seizures, and coma; death normally ensues in the first week of life, but three patients have survived for six, eight, and 15 months respectively.¹ In patients with a partial defect these symptoms may be less severe or delayed until later in infancy and usually result in mental retardation and major neurological defects.

Treatment of carbamyl phosphate synthetase I

deficiency used to be protein restriction or replacement of amino acids by their ketoanalogues.² Brusilow *et al* suggested treatment based on stimulating alternative pathways of nitrogen excretion³ by administering sodium benzoate and sodium phenylacetate. We describe a 15 month old patient with almost complete deficiency who has been treated from birth, with good results.

Case history

This girl, born at term of birthweight 2800 g, is the fourth child of healthy non-related parents. The first child, a boy, who had become lethargic and had fed poorly from the second day of life, was admitted to the intensive care department because of respiratory problems and coma on day 3, and died within 24 hours. Plasma amino acid determinations had shown a very low concentration of citrulline and very high values for glutamine; in urine the concentration of orotic acid was not increased. A urea cycle enzyme disorder, particularly carbamyl phosphate syn-

thetase I or ornithine transcarbamylase deficiency, was suspected but could not be confirmed since no liver tissue was available. No abnormalities were found in the second and third children (both girls) by metabolic screening immediately after birth.

In our patient the plasma ammonia concentrations in cord blood and 6 hours after birth were normal, so feeding was started with a milk formula similar in composition to human milk. After 12 hours, however, the plasma ammonia concentration rose to 158 $\mu\text{mol/l}$ (268.6 $\mu\text{g}/100\text{ ml}$) (normal range 40 to 100 $\mu\text{mol/l}$ (68 to 170 $\mu\text{g}/100\text{ ml}$)) and after 30 hours to 210 $\mu\text{mol/l}$ (357 $\mu\text{g}/100\text{ ml}$). Citrulline in plasma was undetectable; glutamine was raised (1810 $\mu\text{mol/l}$ (26.5 $\text{mg}/100\text{ ml}$) normal range 400 to 800 $\mu\text{mol/l}$ (5.8 to 11.6 $\text{mg}/100\text{ ml}$)).

Orotic acid excretion was normal. As carbamyl phosphate synthetase I deficiency was suspected treatment with sodium benzoate (250 $\text{mg}/\text{kg}/\text{day}$) was started, and on day 4 an alternative feed was given, consisting of a non-protein formula (Mead Johnson no 80056) providing 100 $\text{kcal}/\text{kg}/\text{day}$ with

Figure Management and weight gain of the patient during the study period.

0.6 g/kg essential amino acids (including arginine HCl) (see Figure).

Plasma ammonia and glutamine concentrations returned to normal and after three weeks the previous milk formula was added to this diet in increasing amounts. The plasma ammonia fell to very low concentrations and sodium benzoate treatment was gradually withdrawn. Shortly thereafter the infant started vomiting and her plasma ammonia concentration increased to 180 $\mu\text{mol/l}$ (306 $\mu\text{g}/100\text{ ml}$). The protein intake was reduced and she recovered quickly. Citrulline (1 mmol/kg/day) was added to the diet to stimulate the urea cycle.

To confirm the diagnosis enzyme activity was measured. In leucocytes normal activity was found, in rectal mucosa the activity was 50% of normal, while in liver tissue carbamyl phosphate synthetase I activity was 5% of normal.⁴

One episode of food refusal and hyperammonaemia (230 $\mu\text{mol/l}$ (391 $\mu\text{g}/100\text{ ml}$)) occurred at 3½ months due to an upper respiratory tract infection. An intravenous bolus injection of sodium benzoate (250 mg/kg/30 min) was sufficient to restore metabolic balance. The plasma ammonia concentration increased slightly when the child was 7 months old, whereupon sodium benzoate treatment was reinstituted and milk protein was temporarily withdrawn. Her plasma ammonia concentration became normal, but three weeks later hyperammonaemia (368 $\mu\text{mol/l}$ (625.6 $\mu\text{g}/100\text{ ml}$)) and drowsiness occurred. Large amounts of hippuric acid and little free benzoate were found in urine. Protein intake was completely withdrawn and an intravenous bolus injection of sodium benzoate was given twice. Thereafter she remained normoammonaemic on a low protein diet. At 10 months she had severe diarrhoea so all oral feeding and sodium benzoate treatment were temporarily withdrawn. As she had failed to gain weight since the age of 7 months, despite a high energy diet, sodium phenylacetate (125 mg/kg/day) was added to the treatment. From that time on we were able to increase the protein intake and she gained weight rapidly.

The child is now 15 months old. Her weight, length, and head circumference are on the 25th centile and psychomotor development is normal (Griffith test: DQ 107).

Discussion

Early treatment is the most important factor in preventing irreversible brain damage in hyperammonaemia. After the initial increase in plasma ammonia our patient was treated as having an urea cycle enzyme deficiency. Absence of plasma citrulline and normal excretion of orotic acid in urine

suggested carbamyl phosphate synthetase I deficiency. Estimation of carbamyl phosphate synthetase activity in rectal mucosa and in leucocytes is not conclusive confirmation, because carbamyl phosphate synthetase activity (the cytosolic enzyme necessary for synthesis of pyrimidines) is type II in these tissues (Berger R, unpublished data). A liver biopsy should be performed for determination of carbamyl phosphate synthetase I activity.

In the first 7 months of life a protein restricted diet supplemented with essential amino acids proved to be sufficient to maintain normoammonaemia, with normal growth and development. Thereafter the relatively high tolerance of protein decreased dramatically and only continuous treatment with sodium benzoate and sodium phenylacetate could meet the protein requirement necessary for adequate growth. The reason for this decrease in protein tolerance is not clear. It cannot be explained by the decreasing growth velocity because in that case a proportional reduction of protein intake would have been sufficient to maintain growth without hyperammonaemia. Nor could increases in the plasma ammonia concentration be attributed to failure of the alternative pathways for nitrogen excretion, because high concentrations of the metabolites were found in urine.

This case re-emphasises that if a child dies in the first days of life without apparent cause, one should consider the possibility of a urea cycle enzyme deficiency among other inborn errors of metabolism. Subsequent siblings should be screened immediately after birth and treatment should be started as soon as increased plasma ammonia concentrations are found.

We thank Dr S W Brusilow (Johns Hopkins Medical Institute) for his support during the treatment.

References

- Walser M. Urea cycle disorders and other hereditary hyperammonemic syndromes. In: Stanbury JB, Wijnngaarden JB, Frederickson DS, Goldstein JL, Brown MS, eds. *The metabolic basis of inherited disease*. New York: McGraw-Hill, 1983:414-6.
- Batshaw ML, Brusilow S, Walser M. Long term management of a case of carbamyl phosphate synthetase deficiency using ketoanalogues and hydroxylanalogues of essential amino acids. *Pediatrics* 1976;**58**:227-35.
- Batshaw ML, Brusilow S, Walser L, et al. Treatment of inborn errors of urea synthesis. *N Engl J Med* 1982;**306**:1387-92.
- Brown GW, Cohen PP. Comparative biochemistry of urea synthesis. I. Methods for the quantitative assay of urea cycle enzymes in the liver. *J Biol Chem* 1959;**234**:1769-74.

Correspondence to Dr M van de Bor, University Hospital, Department of Paediatrics, Neonatal Unit, Building 35, Rijnsburgerweg 10, 2333 AA Leiden, The Netherlands.

Received 26 June 1984