WKY Chan 陳桂如
WM But 畢慧文
CW Law 羅志偉

Ammonia detoxification by continuous venovenous haemofiltration in an infant with urea cycle defect

對一名尿素循環病患嬰兒通過連續靜靜脈血過濾進行的氨解毒

We report the case of a newborn baby with carbamoyl phosphate synthetase deficiency. He presented at 2 weeks of life, deteriorating to a state of hyperammonaemic coma and respiratory failure. Rapid detoxification was successfully achieved by continuous venovenous haemofiltration while a definitive diagnosis and treatment were determined. The ammonia clearance achieved by continuous venovenous haemofiltration was greater than 20 mL/min/m², which is superior to that achieved by peritoneal dialysis and arteriovenous haemofiltration in this age-group.

我們報告了一個新生兒氨基甲錘磷酸鹽合脢缺乏的病例。他出生2周發病，病況惡化至高氨昏迷和呼吸衰竭狀態。在確診並確定治療方案的同時，我們通過連續靜靜脈血過濾，成功地將高氨快速解毒。通過連續靜靜脈血過濾完成的氨清除高於20 mL/min/m²，在這年齡組別中，這個結果較通過腹膜透析和動靜脈血過濾完成的氨清除優勝。

Introduction

Carbamoyl phosphate synthetase deficiency is a rare urea cycle defect, with consequent hyperammonaemia, which is a medical emergency in the newborn. The mortality of neonatal hyperammonaemic coma is high and the overall survival rate reported approximately 70%.[1] Rapid detoxification plays a critical role in preventing and minimising damage to the brain and other organs.[2] We report on a newborn baby with carbamoyl phosphate synthetase deficiency who presented at 2 weeks old and required rapid detoxification following hyperammonaemic coma and respiratory failure.

Case report

A Nepalese newborn presented to the Queen Elizabeth Hospital with an unstable body temperature and cyanosis which was noted during oral feeding at day 2. He was delivered at full-term (2.5 kg) by Caesarean section, and had an Apgar score of 8 at 1 minute and 9 at 5 minutes. Antenatal history was unremarkable and his parent's marriage was non-consanguineous. Initial physical examination was uneventful.

At 48 hours of life, the infant developed repeated tonic-clonic convulsions with apnoeic attacks. The seizures were controlled by the administration of intravenous phenobarbitone and phenytoin, and he was supported by assisted ventilation. His oral feeding was suspended. Initial investigations showed a normal white cell count. Serum sodium, potassium, calcium, and blood sugar levels were normal. Blood, urine, and cerebrospinal fluid cultures were all negative. Electroencephalography showed an encephalopathic picture. The infant's first computed tomography (CT) scan of the brain on day 2 revealed diffuse cerebral oedema. With a presumptive diagnosis of clinical sepsis, penicillin G 100 000 units/kg and cefotaxime 50 mg/kg were given every 12 hours. The patient's conscious state improved and he was successfully extubated at day 5 of life. A repeated CT brain scan on day 5 showed resolution of the

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Department of Paediatrics, Queen Elizabeth Hospital, 30 Gascoigne Road, Hong Kong
WKY Chan, MRCP, FHKAM (Paediatrics)
WM But, MRCP, FHKAM (Paediatrics)
CW Law, MRCP, FHKAM (Paediatrics)

Correspondence to: Dr WKY Chan

cerebral oedema. Enteric feeding was resumed through a nasogastric tube. The infant's feeds were well tolerated but he became progressively lethargic, hypotonic, and was comatose on day 14. Emergent blood tests for plasma ammonia showed an excessively elevated level of greater than 700 μmol/L (normal range, 11-32 μmol/L). Plasma glutamine was 1380 μmol/L (normal range, 420-700 μmol/L), glycine 419 μmol/L (normal range, 120-560 μmol/L), and alanine 668 μmol/L (normal range, 210-661 μmol/L). Gas chromatographic analysis of urinary organic acids showed normal orotic acid. A clinical diagnosis of urea cycle defect was made and all dietary and intravenous nitrogen intake was discontinued and replaced by a 10% dextrose infusion. The patient was given intravenous sodium benzoate 750 mg over 90 minutes followed by a continuous infusion of sodium benzoate 750 mg over a further 24 hours. Arginine 500 mg orally was given every 8 hours as empirical treatment and continuous venovenous haemofiltration (CVVH) was used for ammonia detoxification. The infant's body weight was 3 kg at this time.

A haemofiltration machine (Gambro AK10, Gambro, Sweden) with a neonatal-size blood pump and blood line and a total priming volume of 24 mL, was used for detoxification. A haemofilter (Gambro FH22, Gambro Dialysatoren GmbH & Co. KG, Hechingen, Germany) with a surface area of 0.16 m^2 and a priming volume of 11 mL was selected. A French 5 single lumen catheter measuring 5 cm in length was inserted into each of the femoral veins. Abdominal X-ray confirmed that the left femoral catheter was in the left common iliac vein and the right femoral catheter was in the inferior vena cava. To avoid the recirculation of blood, the distal catheter (left femoral) was used as the 'arterial' end of the system, while the proximal catheter (right femoral) served as the 'venous' end. Since the estimated circulating blood volume of the patient was only 240 mL, the whole CVVH system was primed with packed cells. The pump rate was adjusted and maintained at 150 mL/min, corresponding to a calibrated blood flow rate of 20 mL/min. The ultrafiltration rate was controlled by an infusion pump (IVAC, IVAC Corporation, US). The commencing rate was 300 mL/hr, which was increased to 450 mL/hr as the procedure was well tolerated. The mean ultrafiltration rate achieved was 6.7 mL/min. Replacement solution was prepared by mixing 1 L of 0.45% sodium chloride with 40 mL 8.4% sodium bicarbonate, 40 mL 5.85% sodium chloride, 1 mL 15% potassium chloride, 1 mL 50% magnesium sulphate, and 1 mL potassium phosphate. The final solution had a sodium concentration of 145 mEq/L, potassium 4 mEq/L, bicarbonate 40 mEq/L, and magnesium 1.5 mEq/L. Calcium chloride was added to the maintenance solution. Bicarbonate-based, rather than lactate-based solution was used as the replacement solution in order to minimise the potential risk of lactate acidosis arising from ineffective utilisation of lactate by the immature newborn liver. The system was prediluted with normal saline given at 50 mL/hr (ie 10%-15% of the ultrafiltration rate), and replacement fluid was given at the post-haemofilter line.

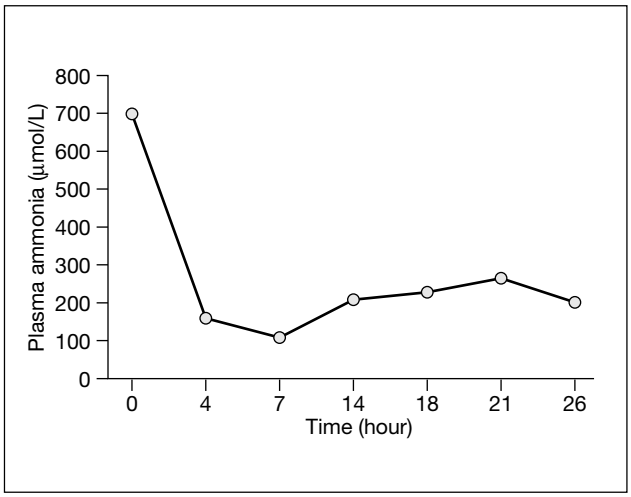

Fig 1. The rapid decrease in plasma ammonia achieved after 6 hours of haemofiltration

Redistribution of tissue ammonia back into the intravascular compartment led to a rebound in plasma ammonia level at 21 hours. Plasma ammonia level was subsequently maintained below 200 μmol/L with the use of arginine and sodium benzoate prior to reaching the definitive diagnosis

All infusion fluids were warmed by a fluid warming system (Hot-Line, SIMS Level 1, Inc., US) before return to the patient and the whole system was heparinised by sodium heparin infused at 15 unit/kg/hr. Urine output was maintained at 12 mL/kg/hr. The net ultrafiltration was targeted at zero balance during the therapy. Plasma ammonia decreased from greater than 700 mmol/L to 156 mmol/L after 4 hours of therapy. The system clotted during the sixth hour of treatment when the infant regained consciousness and started struggling. Continuous venovenous haemofiltration was then stopped as the plasma ammonia level was 105 μmol/L (Fig 1). Estimated ammonia clearance using the Wiegand et al[3] formula ([($NH_3^{predialysis}$ – $NH_3^{postdialysis}$) x bloodflow]/$NH_3^{predialysis}$) was greater than 20 mL/min/m^2. No major disturbance in vital signs was observed (Fig 2). However, treatment was complicated by hyperglycaemia due to the large amount of replacement fluid infused, with each litre containing 25 g of glucose. Blood glucose reached 32.2 mmol/L and insulin infusion was commenced. The child was then successfully extubated 14 hours later. In order to avoid further protein breakdown, a high caloric intake of 80-100 calories/kg/day was provided parentally with 15% dextrose and 20% lipofundin.

Subsequent enzyme study of liver tissue obtained by open biopsy confirmed the diagnosis of carbamoyl phosphate synthetase deficiency. The child was managed with a protein restriction of 0.7 g/kg/day, supplemented with essential amino acids (0.7 g/kg/day), sodium phenylbutyrate (550 mg/kg/day), and citrulline (0.17 g/kg/day). When reassessed at 6 months old, his head circumference was 1.5 cm below the third percentile, while body weight and length were at the tenth percentile. The neurological examination showed a slight increase in muscle tone and his developmental milestones were delayed by approximately 2 months.

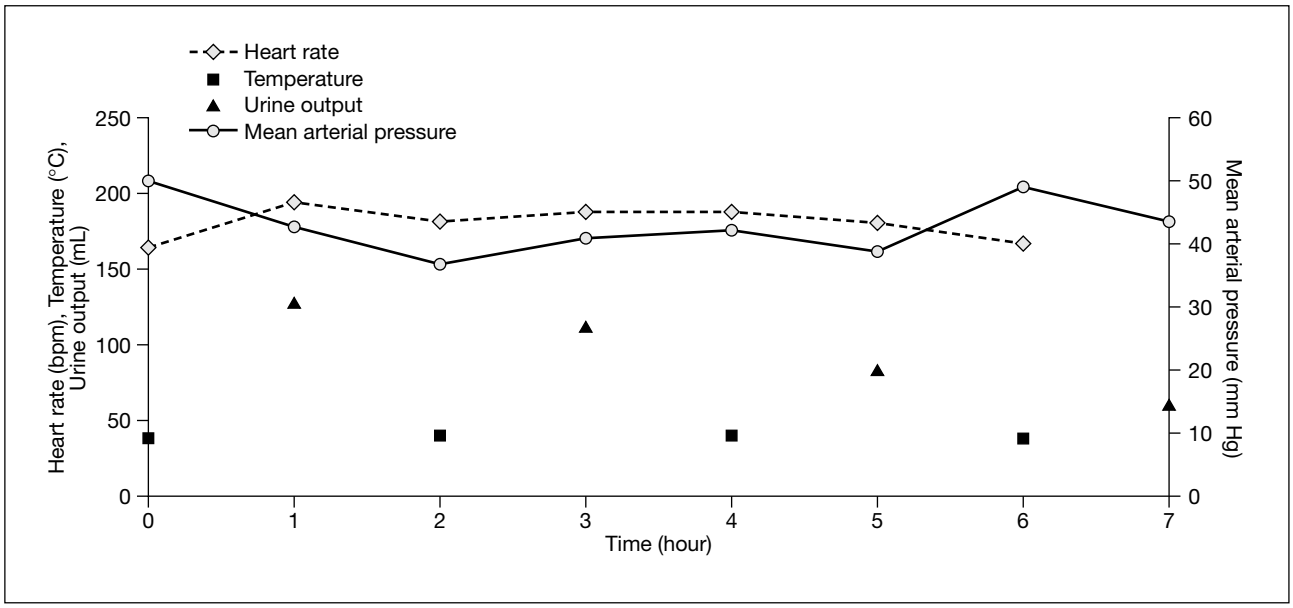

Fig 2. Vital signs during haemofiltration

Mean arterial blood pressure decreased slightly, with a compensatory increase in heart rate during the first hour of therapy. Subsequent vital signs were stable throughout the procedure. Temperature was maintained within the optimal range and urine output was satisfactory throughout

Discussion

The clinical presentation of this patient resembled an ongoing septic process. His neurological condition was seen to improve and then deteriorate following the introduction of enteric feeding. His condition became critical when he developed hyperammonaemic coma and respiratory failure. Hyperammonaemia is a medical emergency—the higher the level of ammonia, the lower the chance of survival and the poorer the neurological outcome. Rapid detoxification is essential and can be achieved by exchange transfusion, peritoneal dialysis, haemofiltration, or haemodialysis, with varying effect on ammonia clearance.[3,4]

Although increasing the volume and cycles of blood exchanged can enhance ammonia clearance, exchange transfusion remains an ineffective method for detoxification because ammonia is distributed throughout the total body water space and the intravascular component represents only a fraction of the total load.[4] Haemodialysis should be the fastest means of ammonia removal and ammonia clearance with haemodialysis has in fact been reported to be 10 times that of peritoneal dialysis.[3,5] Rutledge et al[5] reported an ammonia clearance rate of 84 mL/min/m^2 by haemodialysis, with a blood flow rate of 50 mL/min. However, in a critically ill infant with a body weight of 3 kg there are potential technical difficulties, and infant haemodialysis is not a readily available treatment option in this locality. Peritoneal dialysis is a relatively safe and lenient procedure for an infant; however, clearance of ammonia with this approach is not satisfactory. Wong et al[6] reported an ammonia clearance of 2.15 mL/min/m^2 by peritoneal dialysis. The ammonia clearance improved to 10.55 mL/min/m^2 when they substituted peritoneal dialysis with continuous arteriovenous haemodiafiltration and the ammonia level was reduced to less than 300 mmol/L within 36 hours of therapy. It would be desirable to further accelerate the rate of ammonia removal. Of haemofiltration techniques available, CVVH is considered superior to continuous arteriovenous haemofiltration, and a higher ammonia clearance rate of 19.4 mL/min/m^2 has been reported with this approach.[7] The procedure requires more technical support, but can be performed at the bedside of a ventilated baby and can be supported by the staff in a neonatal intensive care unit. Continuous haemofiltration has the advantage of maintaining stable vital signs and is crucial in managing an ill and small infant. It is also superior to intermittent therapy in achieving the steady removal of ammonia, minimising extreme fluctuations in plasma ammonia level.[7]

During the process of haemofiltration, ammonia together with low molecular weight amino acids was removed from the baby. It was estimated that amino acid concentrations in the ultrafiltrate averaged approximately 80% of those in plasma once CVVH was established. Thus, administration of an intravenous amino acid preparation to normalise serum levels may be necessary if prolonged therapy is anticipated.[8]

Smooth operation of the procedure requires a secured vascular access. Two single lumen catheters serving as the 'arterial' and 'venous' ends of the system were inserted into the femoral veins—note, the shorter the catheter, the lower the resistance. Blood pressure was monitored via an umbilical arterial line. In order to maintain stable haemodynamics, a large amount of replacement fluids were given. Hypothermia is an important complication that should not be underestimated in small babies. In this patient, a warming system provided active warming of the patient line

all the way to the patient connection. This protected the patient line from exposure to cold and eliminated patient line 'cool-down'. The patient's body temperature was thus maintained in the optimal range even when the replacement fluid was infused at a rate of 250 mL to 400 mL/hr. Electrolyte disturbances including hypocalcaemia and hypokalaemia, and hypoglycaemia were predictable complications. Regular blood tests with adjustment of the composition of replacement fluid is thus mandatory.

Finally, the nutrition and caloric intake of the baby should be carefully adjusted. Sufficient protein and energy is necessary for growth and prevents the metabolic perturbation associated with hyperammonaemia and hyperglutaminaemia.[9] In contrast, prolonged fasting will enhance protein breakdown and the metabolic disturbance may overwhelm the clearance capacity of haemofiltration.

Conclusion

Continuous venovenous haemofiltration is an effective alternative to haemodialysis in ammonia detoxification. It can be safely performed in small and critically ill infants. Meticulous monitoring of fluid balance, electrolyte disturbances, hyperglycaemia, and hypothermia is essential during the procedure.

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