Successful extracorporeal treatment of a male with hyperammonaemic coma

Maria Haller1, Angelika Henzler-Le Boulanger2, Jörn Oliver Sass1, Matthias Brandis1 and Lothar Bernd Zimmerhackl1

1Zentrum für Kinderheilkunde und Jugendmedizin, Albert-Ludwigs-Universität, Freiburg und 2Kinderklinik, Kliniken des Landkreises Lörrach, Lörrach, 3Klinik für Kinder- und Jugendheilkunde, Med. Univ. Innsbruck, Germany

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Introduction

Children with urea cycle disorders present with hyperammonaemia and its non-specific symptoms. Acute hyperammonaemia is a medical emergency as the developmental and neurological outcome depends on the duration of hyperammonaemic coma [1]. The longer endogenous protein catabolism continues, the more ammonia will be produced and accumulate and the greater is the risk of coma. To minimize permanent brain damage, early diagnosis and appropriate therapy is mandatory. With diagnosis of hyperammonaemia, it is essential to differentiate between urea cycle defects and other causes of encephalopathy. In Figure 1 a practicable flowchart for establishing the correct diagnosis is depicted [2]. The emergency therapy in children with inborn metabolic disorders presenting with acute hyperammonaemia includes protein restriction, high caloric nutrition using carbohydrates and (later on) lipids, and activation of alternative nitrogen pathways by administration of sodium benzoate and/or phenylbutyrate/phenylacetate. Arginine supplementation can replenish urea cycle substrates. Additionally, essential amino acids should be given. Renal replacement therapy is indicated in cases of rising ammonia levels despite intensive therapy and has been proposed (without established evidence for this value) as an indication if ammonia levels are >400μmol/l.

Case

A male newborn (37 weeks of gestation, birth weight 2860 g, length 50 cm) was admitted to hospital due to symptoms of vomiting, temperature instability, arterial hypertension and hyperexcitation on the second day of life. The next morning, he developed impaired consciousness and muscular hypotonia; extensive diagnostic procedures were conducted and revealed an ammonia level of 406μmol/l and a lactate level of 2.5mmol/l. The patient showed a mild respiratory alkalosis with normal electrolytes. Prothrombin time (PTT) and international normalized ratio (INR) were elevated (PTT 41 s, INR 1.8). Restriction of natural protein was initiated. Emergency measures were taken by administration of sodium benzoate to activate alternative nitrogen waste pathways, and administration of arginine and high dosage intravenous glucose to stop catabolism and to keep the urea cycle at high throughput. The diagnosis of citrullinaemia with a plasma citrulline of 2827μmol/l and plasma glutamine of 3777μmol/l was established. Despite this therapy, the serum ammonia level rose during the following hours to 609μmol/l and the lactate to 4mmol/l. The same day, the infant was transferred to our university hospital which has specialized units for dialysis and inborn errors of metabolism for further treatment. On admission, the baby was stuporos with muscular hypertension. Laboratory tests showed a venous pH of 7.36, normal values for electrolytes, albumin, alanine aminotransferase and blood cell count. The creatinine concentration was 106.96 μmol/l on day 3, and the total
bilirubin was 152.19 μmol/l (age-adapted normal value: up to 205 μmol/l). The serum ammonia showed a level of 874 μmol/l (normal value: up to 40 μmol/l). After appropriate vascular access, haemodiafiltration (HDF) was started [blood flow rate 45–65 ml/min, dialysate flow rate 1000 ml/h (dialysator: Baxter BM 11, filter: Cobe 100), dialysate bath: HF-BIC 35-010, bicarbonate haemofiltration solution, Fresenius Medical Care].

At that point, the serum ammonia level was 1223 μmol/l. After 4.5 h of HDF, the serum ammonia level had decreased to 588 μmol/l (see Figure 2).

A new prescription of HDF was chosen because of an immediate rebound of the serum ammonia level to 688 μmol/l ~1–2 h after stopping HDF. After the following 2 h of HDF, the serum ammonia level decreased to 89 μmol/l. In combination with the above-mentioned nutritional management and the supplement of medication, the serum ammonia concentration did not rise above 30–50 μmol/l during the next 7 days (Figure 3). Dialysis was no longer necessary. With the clearance of ammonia by dialysis, the patient clinically improved immediately: he regained consciousness at the end of dialysis and had a normal muscular tonus. The electroencephalograph (EEG) showing initially general suppression also improved within several days. The patient is now 22 months old and appears to have a normal neurological development under continuous management. Feeding is performed via a percutaneous gastrostomy fistula.

**Comments**

The initial therapeutic modality for rapid correction of acute hyperammonaemia in children with inborn metabolic disorders is protein restriction combined with high caloric nutrition (glucose up to 30–35 g/kg/day) via a central venous line to stop endogenous protein catabolism. In combination with the halting of catabolism and activation of alternative nitrogen waste pathways, renal replacement therapy is mandatory for treatment of acute hyperammonaemia [3]. Peritoneal dialysis (PD) provides insufficient clearance of ammonia, while haemodialysis (HD) leads to a significantly higher and more rapid reduction of ammonia as a result of higher dialysance. In Figure 3, a mathematical exponential one-compartment model, as used in pharmacodynamic studies and the description of dialysance characteristics, was used to describe the behaviour of serum ammonia with regard to the

**Fig. 1.** Flowchart for the differential diagnosis of hyperammonaemia (CPS = carbamyl phosphate synthetase deficiency; NAGS = N-acetylglutamate synthetase deficiency; OTC = ornithine transcarbamylase deficiency; AG = arginase deficiency; ASS = argininosuccinate synthetase deficiency; ASL = argininosuccinate lyase deficiency. The diagnostic path in our patient is marked in red (figure adapted from [2]).

**Fig. 2.** Course of the serum ammonia level in our patient during haemodiafiltration (HDF) combined with protein restriction, high caloric nutrition and administration of sodium benzoate, phenylacetate and arginine.

**Fig. 3.** Mathematical exponential one-compartment-model for the elimination of ammonia during peritoneal dialysis and haemodialysis [C(t) = C0(CAT) × e^(-CL × t/V)], 1 g protein = 33 mM NH3; CAT = catabolism (% of energy demand provided by protein); V = 0.58; onset concentration 500 μM/l NH3]. All underlying dialysances correspond to literature data. There is an assumption of 0% endogenous protein catabolism.
different dialysances of PD, HD and HDF. During HD and HDF, the serum ammonia level dropped much faster than during PD. Furthermore, assuming that a catabolic state is present and 0.5% of the energy demand is provided by protein catabolism, the situation would be even more aggravated in favour of HD (not shown as the figure). Due to the high volume filtered during HDF, this form of dialysis allows a higher infusion rate enabling administration of large amounts of calories as an intravenous infusion to prevent or to interrupt catabolism.

Teaching points

i. For a good neurological outcome of patients with a hyperammonaemic coma, early diagnosis and rapid initiation of therapy including dialysis is mandatory.

ii. Due to a better ammonia clearance (dialysance) and the additional possibility to administer high levels of intravenous fluid replacement, which allows high caloric nutrition, HDF should be used. PD is insufficient because of significantly lower clearance characteristics.

iii. Special care should be taken to use appropriate equipment for the size of the patient (low extracorporeal blood volume, small filter with low filter volume, etc.). Therefore, it is important to transfer patients with severe hyperammonaemia as soon as possible to a specialized centre, where HDF and monitoring of ammonia and amino acids can be performed.

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References


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