Medical Management and Dialysis Therapy for the Infant With an Inborn Error of Metabolism

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Summary: Optimal care of the neonate with hyperammonemia requires expertise in the evaluation, medical management, and decision to initiate dialytic therapy, and therefore compels expeditious collaboration between neonatal intensive care physicians, medical geneticists, and pediatric nephrologists. Neonatal and dialysis nursing expertise also is paramount for the successful provision of dialysis therapy in this setting. The current article addresses the underlying causes, medical management strategies, and dialytic therapy considerations in caring for the neonate with hyperammonemia.
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Neonatal hyperammonemia may be caused by primary defects of one of the enzymes of the urea cycle (UC), by organic acidurias (OA), in which intramitochondrial accumulation of abnormal coenzyme A (CoA) esters inhibits the UC, or, more rarely, by a transient defect of UC as in transient hyperammonemia of the neonate, which sometimes occurs in premature infants. Hyperammonemia also may occur in inherited defects of fatty acid oxidation but it usually is associated with hypoketotic hypoglycemia.

A routine work-up for hyperammonemia should be undertaken if the plasma ammonium level is greater then 150 μmol/L.[1,2] When hyperammonemia is found in a neonate, after ruling out vascular or parenchymal liver dysfunction, the presence of acidosis, increased anion gap, ketonuria, and abnormal blood cell counts is strongly suggestive for an OA, whereas alkalosis with low blood urea nitrogen are found more typically in UC defects (UCD).[1] A definite diagnosis is made by the specific biochemistry work-up. Tandem mass spectrometry, high-performance liquid chromatography, and gas chromatography/mass spectrometry allow acyl-carnitine, organic acids, and amino acids analysis.[3]

PHARMACOLOGIC-DIETARY TREATMENT

A pharmacologic-dietary protocol must be instituted rapidly in parallel with the diagnostic work-up to prevent brain injures and death, regardless of the cause of hyperammonemia.[4,5] The emergency treatment has 3 main goals: toxin removal, enzyme induction, and anabolism. Protein intake must be stopped to avoid exogenous sources of nitrogen, and adequate caloric supply is needed to prevent endogenous catabolism. To further promote anabolism and energy utilization, insulin may be added to glucose solution. Because coenzymes of some of the metabolic pathways are affected in OA, vitamin supplementation (eg, thiamine, biotin, and B_{12}) should be tried in all cases, although the neonatal forms of these defects are rarely vitamin-responsive. Based on the known disturbance of the UC by accumulated CoA esters because of inhibition of *N*-acetylglutamate syn-

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thesis, carbamylglutamate has been used successfully in methylmalonic and propionic acidurias as an allosteric activator, resulting in a significant increase in ammonia detoxification.[6,7] Intravenous administration of carnitine is used to buffer the toxic intramitochondrial accumulation of CoA esters in OAs.[8] In most forms of UCDs, arginine synthesis is reduced. Therefore, this amino acid became essential and its intravenous administration is used to promote the UC by replacing a deficient product.[1] Beginning in 1986, we have used a protocol of treatment for hyperammonemic neonates in our institution.[4,5] This protocol consists of avoidance of nitrogen intake, adequate caloric intake (80-120 kcal/kg/d), and intravenous administration of arginine 250 mg/kg every 2 hours (loading dose) plus 250 to 500 mg/kg/d (maintenance), carnitine 1 g (loading dose) plus 250 to 500 mg/kg/d (maintenance), hydroxycobalamin (1 mg/d), and biotin (10 mg/d). Energy is supplied as parenteral glucose and, whenever possible, with nasogastric infusion of protein-free formulas. Insulin is added to maintain blood glucose levels between 100 and 200 mg/dL. Recently, we modified the protocol by adding carbamylglutamate 200 mg/kg (loading dose) plus 100 mg/kg (maintenance). In patients in whom the diagnosis of a UCD still is pending, the use of benzoate to promote alternative pathways for waste nitrogen disposal may be beneficial.[1,9] Essential amino acids must be reintroduced as soon as circulating ammonia levels return close to normal and possibly within 24 hours so as not to induce their release from the patient's protein stores with consequent worsening of the catabolism.[1]

Dialysis therapy should be initiated in patients who do not respond to medical treatment within 4 to 6 hours, and the drugs mentioned earlier must be continued during dialysis, although the consequences of dialysis removal of some of these drugs have not been evaluated fully. Recently, the role of dialysis in the removal of Na-benzoate and phenylacetate has been stressed.[10] The removal of glycine and glutamine by dialysis could be of benefit in patients with UCD.[11]

DIALYSIS OF NH_4

NH_4 Chemistry and Toxicity

Ammonium (NH_4^+) is a small molecule (molecular weight, 17 d) derived from ammonia gas (NH_3) hydration and subsequent dissociation. The NH_3/NH_4^+ equilibrium is dependent on blood pH and the shift from 7.1 to 7.5 in pH value may induce a 4-fold increase of NH_3 that freely diffuses into the cell, resulting in increased neurotoxicity.[12]

Ammonium is a strong neurotoxic metabolite that accumulates in neonates with primary UC disorders and OAs, both per se and via the accumulation of glutamine in the cytosol of astrocytes[13] with cell swelling and brain edema caused by the osmotic action of glutamine.

WHEN TO INITIATE AND WHEN TO DISCONTINUE

A quick reduction of the plasma ammonium level is required to avoid permanent neurologic damage or death. Simultaneous diagnosis of the specific defect and initial medical treatment must proceed simultaneously after the admission. Medical treatment must take into consideration all possible metabolic causes (metabolic cocktail) and is based on specific pharmacologic supplementation aimed at hyperammonemia reduction.[14] Appropriate rehydration is crucial to avoid further catabolism and preserve renal function. Early response to the initial medical treatment (2-4 h) generally is followed by the progressive ammonium level decrease. In our series, all patients showing a decrease of ammonium levels in the first 4 hours of medical treatment did not need dialysis, whereas all patients who underwent dialysis showed an increase of ammonium levels.[4] A 4-hour cut-off point to determine medical management success may represent a useful indication to start dialysis in these patients. However, this 4-hour window should be used to prepare for having dialysis ready in nonresponders (ammonium level increase or persistently ≥500 μmol/L).[15] Dialysis usually is continued until the plasma ammonium level is steadily less than 100 μmol/L. The decision to withdraw dialysis depends on the response to feeding;

we believe it is preferable to restart feeding under dialysis treatment to evaluate possible hyperammonemia rebound before dialysis cessation.

DIALYTIC THERAPY OPTIONS

Small molecules such as ammonium are cleared rapidly by diffusive transport, so intermittent hemodialysis or continuous venovenous hemodialysis (CVVHD) are preferred over hemofiltration or peritoneal dialysis. Adequate catheter performance (blood flow limited by small neonatal catheters diameter) and dialysate flow in CVVHD (5 instead of 2 L/h) are essential to provide optimal ammonium clearance.[16] A typical CRRT prescription for this case at our institution in Italy would include the following: (1) access: a 6.5F, 7-cm, dual-lumen catheter is placed in one femoral vein; (2) modality: CVVHD is performed with a continuous renal replacement therapy (CRRT) machine equipped with neonatal blood lines and a polyethersulfone 0.3-m^2 filter; (3) prime: the circuit is preprimed with warmed packed red blood cells and saline (50 mL-50 mL proportion); (4) CRRT variables: the blood flow rate is set at 30 to 40 mL/min, according to the catheter performance, the dialysis fluid flow rate is set at 5 L/h (83 mL/min); (5) infusions: a continuous infusion of D-fructose-1,6-diphosphate (100 mg/kg/d) is started to compensate for phosphate loss. During dialysis, 10% dextrose solution is continued and a continuous infusion of carnitine (1 g/24 h) is given. Fluid loss is adjusted to obtain a slightly positive fluid balance.

Further technical considerations are discussed in more detail in the Technical Aspects article of this issue.

No published studies have shown an association between a specific dialysis modality and survival rates. Taking also into account that an ammonium concentration decrease is the final result of more than one concomitant event (dialysis efficiency, catabolism reduction, medical treatment, rehydration), local expertise and available facilities remain, at the moment, the main determinant for the choice of dialysis modality.

OUTCOME

Neonatal-onset UCD and OA are characterized by a more severe outcome if compared with late-onset UCD and OA. In our series, we observed a mortality rate of 27.5% at 2 years, but 48% at long-term follow-up evaluation (range, 2-22 y) with no significant difference between UCD and OA, whereas late-onset patients showed only a 10% mortality rate. Similarly, long-term cognitive development worsened in neonatal-onset patients but did not deteriorate in late-onset ones.[5]

The short-term prognosis of neonatal hyperammonemia depends mainly on coma duration[4,17] and peak ammonium level.[4,15] Coma duration longer than 30 hours before dialysis initiation negatively affects the outcome.[4] The role of detoxification rapidity on short-term outcome[16] probably becomes more relevant when coma duration before dialysis is short. These observations emphasize the importance of expeditious diagnosis and a prompt referral of hyperammonemic infants to hospitals with infant dialysis facilities. When the patient has been referred to a tertiary care hospital, the success of this treatment depends on the organization of a multidiscipline team that includes metabolic experts, a skilled pediatric dialysis team, intensivists, laboratory staff, and dieticians.

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