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Urea cycle disorders

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Most patients with urea cycle disorders who present as neonates, do so with deteriorating feeding, drowsiness and tachypnoea, following a short initial period when they appear well. The plasma ammonia should be measured at the same time as the septic screen in such patients. Ammonia levels above 200 µmol/l are usually caused by inherited metabolic diseases and it is essential to make a diagnosis for genetic counselling, even if the patients die. The aim of treatment is to lower the ammonia concentrations as fast as possible. Sodium benzoate, sodium phenylbutyrate and arginine can exploit alternative pathways for the elimination of nitrogen but haemodialysis or haemofiltration should be instituted if ammonia concentrations are >500 µmol/l or if they do not fall promptly. Long-term management involves drugs, dietary protein restriction and use of an emergency regimen during illness. Severe hyperammonaemia is usually associated with irreversible neurological damage, particularly if levels have been above 800 µmol/l for >24 hours, and the option of withdrawing treatment should be discussed with the family.

Key words: ammonia, carbamoyl phosphate synthetase, ornithine transcarbamoylase, citrullinaemia, argininosuccinic aciduria, sodium benzoate, sodium phenylbutyrate

Introduction

The urea cycle is the final common pathway for the excretion of waste nitrogen in mammals (Fig. 1). Urea has low toxicity even at high concentrations, in contrast to its precursors, particularly ammonia. Urea cycle defects presenting in the neonatal period are usually associated with severe and rapidly worsening hyperammonaemia. This is a major emergency in neonates. Early recognition and aggressive treatment are essential to achieve a good outcome. Even with prompt intervention, the prognosis is poor for patients who present with symptoms in the neonatal period. A number of other disorders besides urea cycle defects can cause severe hyperammonaemia but most are inherited and every effort must be made to establish a diagnosis.

Clinical presentation

Patients with urea cycle disorders commonly present in the neonatal period but the symptoms and signs are not specific. Most of these babies are of normal birth weight and are initially healthy, but then after a short interval, that can be less than 24 hours, they become unwell. Common early symptoms are poor feeding, vomiting, lethargy and/or irritability and tachypnoea. The initial working diagnosis is almost invariably sepsis. Rather characteristically, these babies often have a mild but transient respiratory alkalosis at this stage that can be a useful diagnostic clue as there are few other causes in a baby not on a ventilator. They may also have neuro-muscular irritability and stridor but all these symptoms are usually only transient as generally the patients deteriorate rapidly. They

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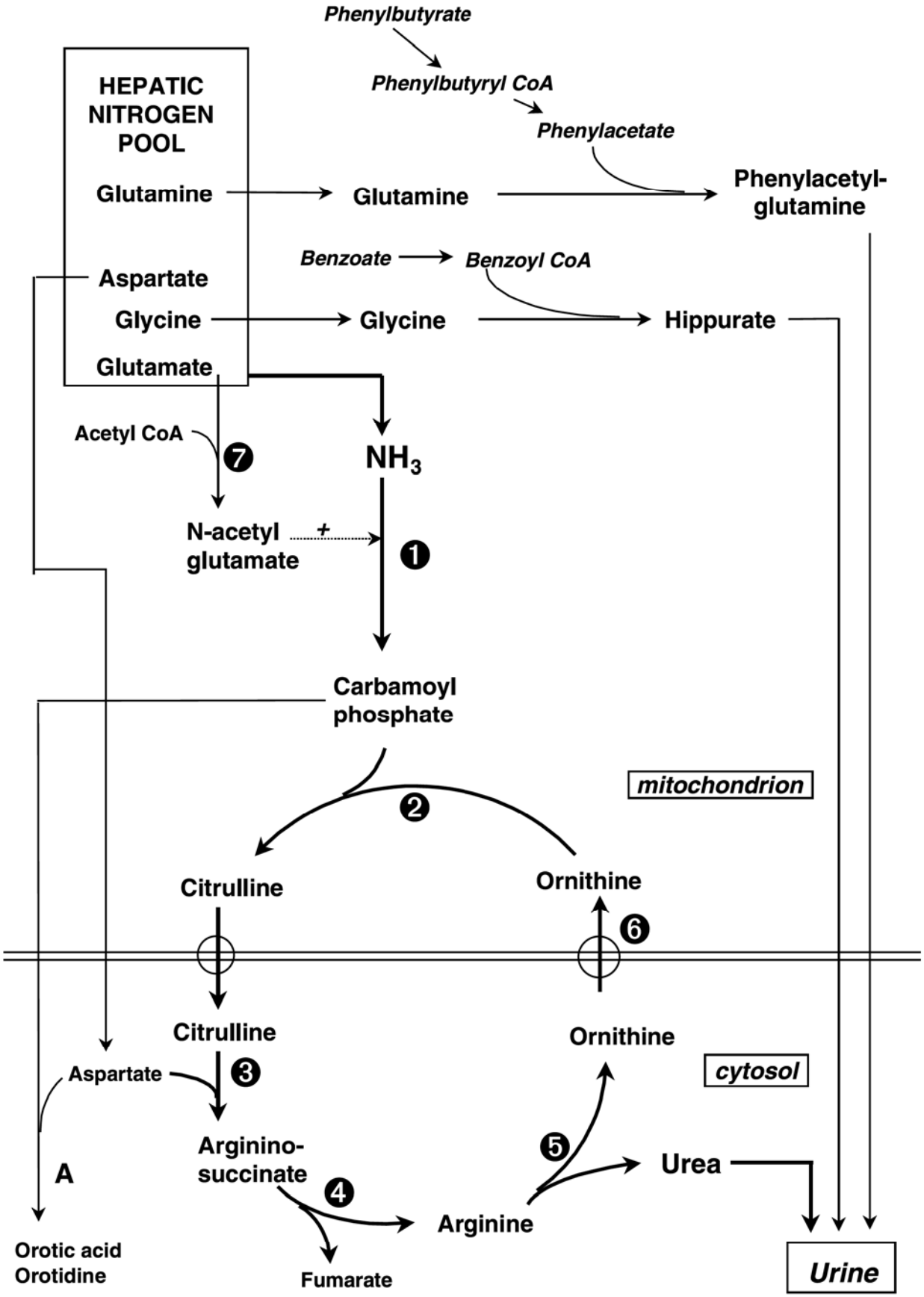

Figure 1. Pathways for the disposal of waste nitrogen. The urea cycle and alternative pathways of nitrogen excretion. Steps in the urea cycle: 1. Carbamoyl phosphate synthetase; 2. Ornithine transcarbamoylase; 3. Argininosuccinate synthetase; 4. Argininosuccinate lyase; 5. Arginase; 6. Mitochondrial ornithine carrier; 7. N-acetyl glutamate synthetase. A: Allopurinol

intensive care. The babies then often develop a wide range of secondary complications such as disordered liver function that obscures the primary condition. Untreated, most babies will die, often with complications such as cerebral or pulmonary haemorrhage. Some survive but they are invariably handicapped, usually severely.

Patients with arginase deficiency usually present after the neonatal period with spasticity in the legs and developmental delay but seldom have symptomatic hyperammonaemia. On the other hand, neonatal hyperammonaemia is well recognized in patients with defects of the mitochondrial ornithine transporter, an essential component of the urea cycle (Hyperornithinaemia, Hyperammonaemia, Homocitrullinuria syndrome). Severe neonatal hyperammonaemia also occurs in patients with ornithine aminotransferase deficiency [1,2], a defect that more commonly presents in adults with cataracts and gyrate atrophy of the choroid and retina.

Differential diagnosis

The differential diagnosis of hyperammonaemia is wide and is summarized in Table 1. The most common differential diagnoses of severe hyperammonaemia are organic acidaemias, particularly propionic and methylmalonic acidaemia. It is important to recognize that patients with these disorders may have marked hyperammonaemia with a respiratory alkalosis without acidosis or ketosis. Transient hyperammonaemia of the newborn (THAN) is an ill-understood condition, possibly related to immaturity of liver metabolism or hepatic vascular disease. Plasma ammonia levels may be very high initially but no underlying metabolic disease is found. Although babies with THAN are often born prematurely with early onset of symptoms [3], it may be difficult to distinguish between urea cycle disorders and this disorder on clinical grounds. The incidence of THAN appears to have been falling over recent years in many centres around the world. Less severe hyperammonaemia is common, both in other metabolic disorders and acquired illness such as sepsis and perinatal asphyxia. Babies with systemic herpes simplex, particularly involving the liver, may have marked hyperammonaemia without obvious signs.

Table 1. Differential diagnosis of hyperammonaemia

Inherited disorders
Urea cycle enzyme defects
Carbamoyl phosphate synthetase deficiency
Ornithine transcarbamoylase deficiency
Argininosuccinate synthetase deficiency (Citrullinaemia)
Argininosuccinate lyase deficiency (Argininosuccinic aciduria)
Arginase deficiency
N-acetylglutamate synthetase deficiency
Transport defects of urea cycle intermediates
Lysinuric protein intolerance
Hyperammonaemia – hyperornithinaemia – homocitrullinuria syndrome
Organic acidurias
Propionic acidaemia
Methylmalonic acidaemia and other organic acidaemias
Fatty acid oxidation disorders
Medium chain acyl-CoA dehydrogenase deficiency
Systemic carnitine deficiency
Long chain fatty acid oxidation defects and other related disorders
Other inborn errors
Pyruvate carboxylase deficiency (neonatal form)
Ornithine aminotransferase deficiency (neonates)
Acquired disorders
Transient hyperammonaemia of the newborn
Any severe systemic illness
Herpes simplex – systemic infection
Liver failure (rare in neonates)
Infection with urease positive bacteria (if urinary tract stasis)

Investigations

Routine tests are not helpful for establishing the diagnosis of hyperammonaemia. The most important diagnostic test in urea cycle disorders is measurement of the plasma ammonia concentration. In healthy neonates plasma ammonia is normally less than 65 μmol/l [4], but may be raised as a result of a high protein intake, difficult venepuncture or a haemolysed blood sample. In sick neonates (for example, those with sepsis or perinatal asphyxia), plasma ammonia concentrations may increase up to 180 μmol/l. Patients with inborn errors presenting in the newborn period usually have concentrations greater than 200 μmol/l, often very much greater.

Ammonia levels can rise rapidly in patients with urea cycle disorders. Thus, plasma ammonia measurement should be repeated after a few hours, even if it is only modestly elevated.

In cases of significant hyperammonaemia, the following investigations should be performed immediately:

- Blood pH and gases
- Plasma urea and creatinine, electrolytes, glucose

Table 2. Diagnostic tests in urea cycle defects

Disorder	Alternative names	Plasma amino acid concentrations	Urine orotic acid	Tissue for enzyme diagnosis	Genetics (chromosome localization)
Carbamoyl phosphate synthetase deficiency	CPS deficiency	↑glutamine ↑alanine ↓citrulline ↓arginine	N	Liver	AR (chromosome 2p)
Ornithine transcarbamoylase deficiency	OTC deficiency	↑glutamine ↑alanine ↓citrulline ↓arginine	↑↑	Liver	X-linked (Xp21.1)
Argininosuccinic acid synthetase deficiency	Citrullinaemia	↑↑citrulline ↓arginine	↑	Liver/Fibroblasts	AR (chromosome 9q)
Argininosuccinic acid lyase deficiency	Argininosuccinic aciduria (ASA)	↑citrulline ↑argininosuccinic acid ↓arginine	↑	RBC/Liver/Fibroblasts	AR (chromosome 7q)
Arginase deficiency	Hyperargininaemia	↑arginine	↑	RBC/Liver	AR (chromosome 6q)
N-acetylglutamate synthetase deficiency	NAGS deficiency	↑glutamine ↑alanine	N	Liver	AR (not confirmed)

AR: autosomal recessive; RBC: red blood cells; N: normal.

- Liver function tests and clotting studies
- Plasma amino acids
- Urine organic acids, orotic acid and amino acids
- Plasma free and acylcarnitines

The plasma amino acids and urine organic acids are very urgent.

In all urea cycle disorders there is accumulation of glutamine and alanine. There are also increased concentrations of the amino acids immediately proximal to the block in the metabolic pathway and decreased concentrations of those beyond the block (Fig. 1). Thus, in citrullinaemia, argininosuccinic aciduria (ASA) and arginase deficiency, the plasma amino acids are usually diagnostic (Table 2).

Orotic acid and orotidine are excreted in excess in the urine if there is a metabolic block distal to the formation of carbamoyl phosphate. In these disorders carbamoyl phosphate accumulates, leaves the mitochondrion and enters the pathway for the de novo synthesis of pyrimidines in the cytosol (Fig. 1). Measurement of urinary orotic acid is particularly helpful for distinguishing ornithine transcarbamoylase (OTC) deficiency from carbamoyl phosphate synthetase (CPS) or N-acetyl glutamate synthetase (NAGS) deficiencies.

Diagnoses can generally be confirmed by measuring the enzyme activity in an appropriate tissue (Table 2). This is the only way to distinguish between CPS and NAGS deficiencies. Assays of CPS are well-established but measurement of NAGS activity is not straightforward. Patients with NAGS deficiency generally show a clinical response to N-carbamyl glutamate, an orally active analogue of N-acetyl glutamate, but this is unreliable for diagnosis because a response is also seen in some patients with CPS deficiency [5].

Other investigations will detect complications. In the late stages of hyperammonaemia patients may have marked disturbances of liver function with disordered clotting, renal failure and hypocalcaemia. In the later stages of hyperammonaemic encephalopathy, brain imaging may show cerebral oedema or intracranial haemorrhage.

If the patient seems likely to die it is essential to collect the appropriate specimens, since otherwise the diagnosis cannot be confirmed:

- Plasma (heparinized, separated and deep frozen)
- Blood spots on filter paper for acylcarnitines
- Urine (deep frozen in a plain tube)
- Blood for DNA (anticoagulated with EDTA and deep frozen)
- Skin for fibroblast culture taken with sterile precautions into medium and stored at 4–8°C, not frozen
- Liver, snap frozen for enzymology

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