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Inborn Metabolic Diseases

Diagnosis and Treatment

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With 66 Figures and 57 Tables

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The Urea Cycle

The urea cycle which, in its complete form, is only present in the liver, is the main pathway for the disposal of excess of ammonium nitrogen. This cycle sequence of reactions, localised in part in the mitochondria and in part in the cytosol, converts the toxic ammonia molecule into the non-toxic product, urea, which is excreted in the urine. There are genetic defects of each of the enzymes of the urea cycle which lead to hyperammonaemia. Some genetic defects of other important metabolic pathways may lead to secondary inhibition of the urea cycle. Alternative pathways for nitrogen excretion, namely conjugation of glycine with benzoate and of glutamine with phenylacetate can be exploited in the treatment of patients with defective ureagenesis.

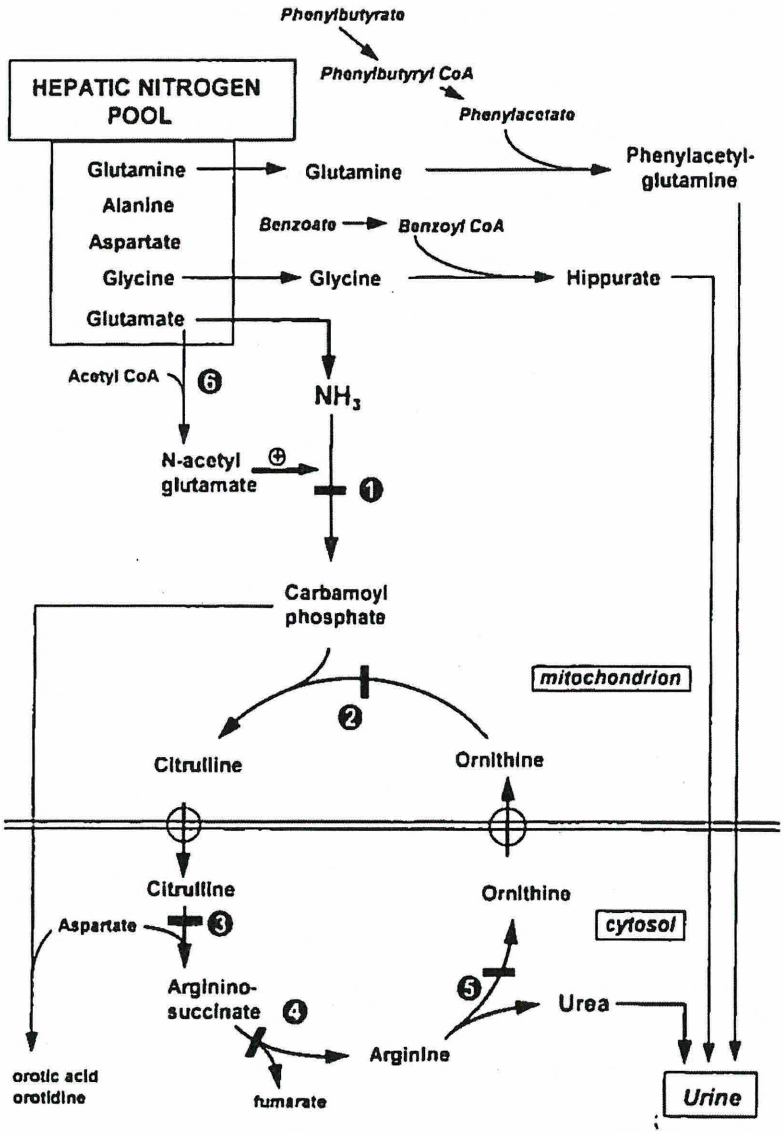

Fig. 17.1. The urea cycle and alternative pathways of nitrogen excretion. Enzymes: 1, carbamoyl phosphate synthetase; 2, ornithine transcarbamoylase; 3, argininosuccinate synthetase; 4, argininosuccinate lyase; 5, arginase; 6, *N*-acetylglutamate synthetase. Enzyme defects are depicted by *solid bars* across the arrows

Disorders of the Urea Cycle

J.V. Leonard

CONTENTS

Five inherited disorders of the urea cycle are now well described. These are characterised by hyperammonaemia and disordered amino-acid metabolism. The presentation is highly variable: those presenting in the newborn period usually have an overwhelming illness that rapidly progresses from poor feeding, vomiting, lethargy or irritability and tachypnoea to fits, coma and respiratory arrest. In infancy, the symptoms are less severe and more variable. Poor developmental progress, behavioural problems, hepatomegaly and gastrointestinal symptoms are usually observed. In children and adults, chronic neurological illness is characterised by behavioural problems, confusion, irritability and cyclic vomiting, which deteriorates to acute encephalopathy during metabolic stress. Arginase deficiency shows more specific symptoms, such as spastic diplegia, dystonia, ataxia and fits. All urea-cycle disorders have autosomal-recessive inheritance except ornithine carbamoyl transferase deficiency, which is X-linked.

Clinical Presentation

Patients with urea-cycle disorders may present at almost any age. However, there are certain times at which they are more likely to develop symptoms because of metabolic stress, such as infection precipitating protein catabolism. These are:

- The neonatal period.
- During late infancy. Children are vulnerable during this period because of the slowing of growth, the change to cow's milk and weaning foods and the declining maternal antibody and consequent development of intercurrent infections.
- Puberty. The changing growth rate and psychosocial factors may precipitate decompensation.

However, it must be emphasised that many patients may present outside these periods. The patterns of the clinical presentation of hyperammonaemia are rather characteristic and are broadly similar for all the disorders except arginase deficiency, which is discussed separately. The early symptoms are often non-specific and initially, therefore, the diagnosis is easily overlooked. The most important points in diagnosing hyperammonaemia are to think of it during diagnosis and to measure the plasma ammonia concentration.

Neonatal Presentation

Most babies with urea cycle disorders are of normal birthweight and are initially healthy but, after a short interval that can be less than 24 h, 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 may have a transient mild respiratory alkalosis, which can be a useful diagnostic clue at this stage. Usually, they deteriorate rapidly, with more obvious neurological and autonomic problems, including changes of tone with loss of normal reflexes, vasomotor instability and hypother-

mia, apnoea and fits. The baby may soon become totally unresponsive and may require full intensive care. Untreated, most babies will die, often with complications, such as cerebral or pulmonary haemorrhage, the underlying metabolic cause for which may not be recognised. Some survive neonatal hyperammonaemia but are invariably handicapped to some degree.

Infantile Presentation

In infancy, the symptoms are generally rather less acute and more variable than in the neonatal period and include anorexia, lethargy, vomiting and failure to thrive, with poor developmental progress. Irritability and behavioural problems are also common. The liver is often enlarged but, as the symptoms are rarely specific, the illness is initially attributed to many different causes that include gastrointestinal disorders (gastro-oesophageal reflux, cow's milk protein intolerance), food allergies, behaviour problems or hepatitis. The correct diagnosis is often only established when the patient develops a more obvious encephalopathy with changes in consciousness level and neurological signs (see below).

Children and Adults

At these ages, the patients commonly present with a more obviously neurological illness.

ACUTE ENCEPHALOPATHY. Whilst older patients often present with episodes of acute metabolic encephalopathy, they may also have chronic symptoms. Usually, symptoms develop following metabolic stress precipitated by infection, anaesthesia or protein catabolism, such as that produced by the rapid involution of the uterus in the puerperium [1]. However an obvious trigger is not always apparent. The patients first become anorexic, lethargic and unwell. Sometimes they are agitated and irritable, with behaviour problems or confusion. Vomiting and headaches may be prominent, suggesting migraine or cyclical vomiting. Others may be ataxic as though intoxicated. On examination, hepatomegaly may be present, particularly in those with argininosuccinic aciduria. The patients may then recover completely but, if not, they may then develop neurological problems, including a fluctuating level of consciousness, fits and (sometimes) focal neurological signs, such as hemiplegia [2] or cortical blindness. Untreated, they continue to deteriorate, becoming comatose, and they may die. Alternatively, they may recover with a significant neurological deficit. The cause of death is usually cerebral oedema.

Between episodes, the patients are usually relatively well, although some, particularly younger ones, may continue to have problems, such as vomiting or poor developmental progress. Some patients may voluntarily restrict their protein intake. In addition to those disorders already mentioned, the illness may be attributed to a wide variety of other disorders, including Reye's syndrome, encéphalitis, poisoning and psychosocial problems.

CHRONIC NEUROLOGICAL ILLNESS. Learning difficulties or more obvious mental retardation are common, and some patients, particularly those with argininosuccinic aciduria, may present with relatively few symptoms apart from mental retardation and fits. About half the patients with argininosuccinic acid have brittle hair (trichorrhexis nodosa). Patients may present with chronic ataxia, which is worse during intercurrent infections [3].

ARGINASE DEFICIENCY. Arginase deficiency commonly presents with spastic diplegia and, initially, a diagnosis of cerebral palsy is almost always suspected. However, the neurological abnormalities appear to be slowly progressive, although it may be difficult to distinguish this from an evolving cerebral palsy. During the course of the disease, fits, ataxia and dystonia may develop. Occasionally, patients may present with an acute encephalopathy or anticonvulsant-resistant fits [4].

Metabolic Derangement

The urea cycle is the final common pathway for the excretion of waste nitrogen in mammals. The steps in the urea cycle are shown in Fig. 17.1. Ammonia is probably derived principally from glutamine and glutamate and is converted to carbamoyl phosphate by *carbamoyl phosphate synthetase* (CPS). This enzyme requires an allosteric activator, *N*-acetylglutamate, for full activity. This compound is formed by the condensation of acetyl coenzyme A (acetyl CoA) and glutamate in a reaction catalysed by *N-acetyl glutamate synthetase*. Carbamoyl phosphate condenses with ornithine to form citrulline in a reaction catalysed by *ornithine transcarbamoylase*. The product, citrulline, condenses with aspartate to produce argininosuccinate in a reaction catalysed by *argininosuccinate synthetase*, and the arginosuccinate is then hydrolysed to arginine and fumarate by *argininosuccinate lyase*. The arginine is itself cleaved by *arginase*, releasing urea and re-forming ornithine. Within the urea cycle itself, ornithine acts as a carrier; it is neither formed nor lost.

Each molecule of urea contains two atoms of waste nitrogen, one derived from ammonia and the other from aspartate. Regulation of the urea cycle is not fully understood, and it is likely that there are several mechanisms controlling flux through this pathway [5].

These include enzyme induction, the concentrations of substrates, intermediates and *N*-acetyl glutamate, and hormonal effects. Defects of each step have now been described and are listed in Table 17.1.

The plasma *ammonia* concentration is raised as a result of metabolic blocks in the urea-cycle. The degree to which it is elevated depends on several factors, including the enzyme involved and its residual activity, the protein intake and the rate of endogenous protein catabolism, particularly if this is increased because of infection, fever or other metabolic stresses. The values may also be falsely elevated if the specimen is not collected and handled correctly.

The concentrations of the amino acids in the metabolic pathway immediately proximal to the enzyme defect will increase, and those beyond the block will decrease (Table 17.1). In addition, plasma alanine and particularly *glutamine* accumulate in all the disorders. The concentration of *citrulline* is often helpful, but it may not always be reliable during the newborn period [6].

Orotic acid and orotidine are excreted in excess in the urine if there is a metabolic block distal to the formation of carbamoyl phosphate, as is the case in ornithine transcarbamoylase (OTC) deficiency, citrullinaemia, argininosuccinic aciduria and arginase deficiency (Fig. 17.1). In these disorders, carbamoyl phosphate accumulates, leaves the mitochondrion and, once in the cytosol, enters the pathway for the de novo synthesis of pyrimidines. The urea cycle is also closely linked to many other pathways of intermediary metabolism, particularly the citric-acid cycle.

Toxicity

Ammonia increases the transport of tryptophan across the blood–brain barrier, which then leads to an increased production and release of serotonin [7]. Some of the symptoms of hyperammonaemia can be explained on this basis, and the dietary tryptophan restriction has reversed anorexia in some patients with urea cycle disorders [8]. Ammonia induces many other electrophysiological, vascular and biochemical changes in experimental systems, but it is not known to what extent all of these are relevant to the problems of clinical hyperammonaemia in man [9].

Using proton nuclear magnetic resonance spectroscopy, glutamine can also be shown to accumulate at high concentrations, both in experimental models and in man in vivo [10]. The concentrations are such that the increase in osmolality could be responsible for cellular swelling and cerebral oedema.

Diagnostic Tests

Biochemical Tests

Routine tests are not helpful for establishing the diagnosis of hyperammonaemia. Plasma transaminases may be elevated; combined with hepatomegaly, this may lead to the erroneous diagnosis of hepatitis.

The most important diagnostic test in urea cycle disorders is measurement of the plasma ammonia concentration. Normally, this is less than 50 μmol/l but may be slightly raised as a result of a high protein intake, exercise, struggling or a haemolysed blood sample. Generally, patients who are acutely unwell with urea cycle disorders have plasma ammonia concentrations greater than 150 μmol/l, and often significantly higher. However, the concentrations may be near normal when patients are well, are early in an episode of decompensation or if they have been on a low-protein, high-carbohydrate intake for some time.

Healthy neonates have slightly higher values [11]. If they are ill (sepsis, perinatal asphyxia, etc.), plasma

Table 17.1. Urea-cycle disorders: biochemical and genetic details

Disorder	Alternative names	Plasma amino acid concentrations	Urine orotic acid	Tissue for enzyme diagnosis	Genetics (chromosome localisation)
CPS deficiency	CPS deficiency	↑ Glutamine; ↑ alanine; ↓ citrulline; ↓ arginine	N	Liver	AR (chromosome 2p)
OTC deficiency	OTC deficiency	↑ Glutamine; ↑ alanine; ↓ citrulline; ↓ arginine	↑↑	Liver	X-linked (Xp21.1)
Argininosuccinic synthetase deficiency	Citrullinaemia	↑↑ Citrulline; ↓ arginine	↑	Liver/fibroblasts	AR (chromosome 9q)
Argininosuccinic lyase deficiency	Argininosuccinic aciduria	↑ Citrulline; ↑ argininosuccinic acid; ↓ arginine	↑	RBC/liver/ fibroblasts	AR (chromosome 7q)
Arginase deficiency	Hyperargininaemia	↑ Arginine	↑	RBC/liver	AR (chromosome 6q)
NAGS deficiency	NAGS deficiency	↑ Glutamine; ↑ alanine	N	Liver	AR (not confirmed)

↑, increased; ↓, decreased; *AR*, autosomal recessive; *CPS*, carbamyl phosphate synthetase; *N*, normal; *NAGS*, *N*-acetylglutamate synthetase; *OTC*, ornithine transcarbamoylase; *RBC*, red blood cell

ammonia concentrations may increase 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. In that case, further investigations (particularly of the plasma amino acid and urine organic acid levels) are urgent. The following investigations should be performed:

- Blood pH and gases
- Plasma chemistry: sodium, urea and electrolytes, glucose and creatinine
- Liver-function tests and clotting studies
- Plasma amino acids
- Urine organic acids, orotic acid and amino acids
- Plasma free and acyl carnitines

In all urea-cycle disorders, there is accumulation of glutamine and alanine and, in citrullinaemia, argininosuccinic aciduria and arginase deficiency, the changes in the amino acids are usually diagnostic (Table 17.1). Orotic aciduria with raised plasma glutamine and alanine concentrations suggests OTC deficiency. The diagnosis of this and the other disorders can be confirmed by measuring enzyme activity in appropriate tissue (Table 17.1). The enzyme diagnosis of *N*-acetyl glutamate synthetase deficiency is not straightforward, and the response to a load of *N*-carbamyl glutamate, an orally active analogue of *N*-acetyl glutamate, may be helpful both diagnostically and for treatment.

Imaging

Patients who present with an acute encephalopathy commonly receive brain imaging at an early stage. This may show no abnormality, a localised area of altered signal or, if the patient is very seriously ill, widespread cerebral oedema [12].

Focal areas of altered signal may be identified and need to be distinguished from herpes simplex encephalitis. A careful history revealing previous episodes of encephalopathy, albeit mild, may provide vital clues. Imaging in patients who have recovered from a severe episode of hyperammonaemia usually show cerebral atrophy that may be focal, particularly in those areas in which there were altered signals during the acute illness.

Differential Diagnosis

The differential diagnosis of hyperammonaemia is wide, and the most common conditions are summarised in Table 17.2. In the neonatal period, the most common differential diagnoses are organic acidaemias, particularly propionic and methylmalonic acidaemia. Patients with these disorders may have had marked hyperammonaemia with minimal metabolic acidosis or ketosis. Although babies with transient hyperammonaemia of the newborn are often born prematurely, with early onset of symptoms [13], it may be difficult to distinguish between urea-cycle disorders and transient hyperammonaemia of the newborn. All patients in whom a tentative diagnosis of Reye's syndrome is made should be investigated in detail for inherited metabolic disorders, including urea-cycle disorders.

Table 17.2. Differential diagnosis of hyperammonaemia

Inherited disorders
Urea cycle enzyme defects
Carbamoyl phosphate synthetase deficiency
Ornithine transcarbamoylase deficiency
Argininosuccinate synthetase deficiency (citrullinaemia)
Argininosuccinate lyase deficiency (arginosuccinic aciduria)
Arginase deficiency
N-acetylglutamate synthetase deficiency
Transport defects of urea cycle intermediates
Lysinuric protein intolerance
Hyperammonemia–hyperornithinemia–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)
Acquired
Transient hyperammonemia of the newborn
Reye's syndrome
Liver failure, any cause (both acute and chronic)
Valproate therapy
Infection with urease-positive bacteria (particularly with stasis in the urinary tract)
Leukaemia therapy, including treatment with asparaginase
Severe systemic illness, particularly in neonates

CoA, coenzyme A

Treatment

The aim of treatment is to correct the biochemical disorder and to ensure that all the nutritional needs are met. The major strategies used are to reduce protein intake, to utilise alternative pathways of nitrogen excretion and to replace nutrients that are deficient.

Low-Protein Diet

Most patients require a low-protein diet. The exact quantity will depend mainly on the age of the patient and the severity of the disorder. Many published regimens suggest severe protein restriction but, in early infancy, patients may need 1.8–2 g/kg/day or more during phases of very rapid growth. The protein intake usually decreases to approximately 1.2–1.5 g/kg/day during pre-school years and 1 g/kg/day in late

childhood. After puberty, the quantity of natural protein may be less than 0.5 g/kg/day. However, it must be emphasised that there is considerable variation in the needs of individual patients.

Essential Amino Acids

In the most severe variants, it may not be possible to achieve good metabolic control and satisfactory nutrition with restriction of natural protein alone. Other patients will not take their full protein allowance. In both these groups of patients, some of the natural protein may be replaced with an essential amino acid mixture, giving up to 0.7 g/kg/day. Using this, the requirements for essential amino acids can be met; in addition, waste nitrogen is re-utilised to synthesise non-essential amino acids, hence reducing the load of waste nitrogen.

Alternative Pathways for Nitrogen Excretion

In many patients, additional therapy is necessary. A major advance in this field has been the development of compounds that are conjugated to amino acids and rapidly excreted [14, 15]. The effect of the administration of these substances is that nitrogen is excreted in compounds other than urea; hence, the load on the urea cycle is reduced (Fig. 17.1). The first compound introduced was sodium benzoate. *Benzoate* is conjugated with glycine to form hippurate, which is rapidly excreted. For each mole of benzoate given, 1 mol of nitrogen is removed. Sodium benzoate is usually given in doses up to 250 mg/kg/day but, in acute emergencies, this can be increased to 500 mg/kg/day. The major side effects are nausea, vomiting and irritability. In neonates, conjugation may be incomplete, with increased risk of toxicity [C. Bachmann, personal communication].

The next drug used was phenylacetate, but this has now been superseded by *phenylbutyrate*, because the former has a peculiarly unpleasant, clinging, mousy odour. In the liver phenylbutyrate is oxidised to phenylacetate, which is then conjugated with glutamine. The resulting phenylacetylglutamine is rapidly excreted in urine; hence, 2 mol of nitrogen are lost for each mole of phenylbutyrate given. Phenylbutyrate is usually given as the sodium salt in doses of 250 mg/kg/day, but has been given in doses of up to 650 mg/kg/day [16]. In a recent study of the side effects [17], there was a high incidence of menstrual disturbance in females. Other problems included anorexia, but it was not easy to distinguish between the effects of the disorder and those of the medicine. Patients are often reluctant to take the medicine, and great ingenuity is sometimes needed to ensure that the patient takes it.

ARGININE AND CITRULLINE. Arginine is normally a nonessential amino acid, because it is synthesised within the urea cycle. For this reason, all patients with urea-cycle disorders (except those with arginase deficiency) are likely to need a supplement of arginine to replace that which is not synthesised [18]. The aim should be to maintain plasma arginine concentrations between 50 µmol/l and 200 µmol/l. For OTC and CPS deficiencies, a dose of 100–150 mg/kg/day appears to be sufficient for most patients. However, in severe variants of OTC and CPS, citrulline may be substituted for arginine in doses up to 170 mg/kg/day, as this will utilise an additional nitrogen molecule. Patients with citrullinaemia and argininosuccinic aciduria have a higher requirement, because ornithine is lost as a result of the metabolic block; this is replaced by administering arginine. Doses of up to 700 mg/kg/day may be needed, but this does have the disadvantage of increasing the concentrations of citrulline and argininosuccinate, respectively. The consequences of this are thought to be less important than those caused by the accumulation of ammonia and glutamine.

OTHER MEDICATION. *Citrate* has long been used to provide a supply of Krebs-cycle intermediates [19]. It is known to reduce postprandial elevation of ammonia and may be helpful in the management of argininosuccinic aciduria [20].

N-carbamyl glutamate can be used in *N*-acetylglutamate synthetase deficiency to replace the missing compound, as it is active orally. The dose is 100–300 mg/kg/day [21]. Patients who respond may require treatment with this compound only. *Anticonvulsants* may be needed for patients with urea-cycle disorders, but sodium valproate should *not* be used, as this drug may precipitate fatal decompensation, particularly in OTC patients [22].

General Aspects of Therapy

All treatment must be monitored with regular quantitative estimation of plasma ammonia and amino acids, paying particular attention to the concentrations of glutamine and essential amino acids. The aim is to keep plasma ammonia levels below 80 µmol/l and plasma glutamine levels below 800 µmol/l [23]. In practice, a glutamine concentration of 1000 µmol/l together with concentrations of essential amino acids within the normal range (see the algorithm, Fig. 17.2) is probably more realistic. All diets must, of course, be nutritionally complete and must meet requirements for growth and normal development.

The concept of balance of diet and medicine is important. The protein intake of the patients varies considerably, and the figures that have been given should be regarded only as a guide. The variation

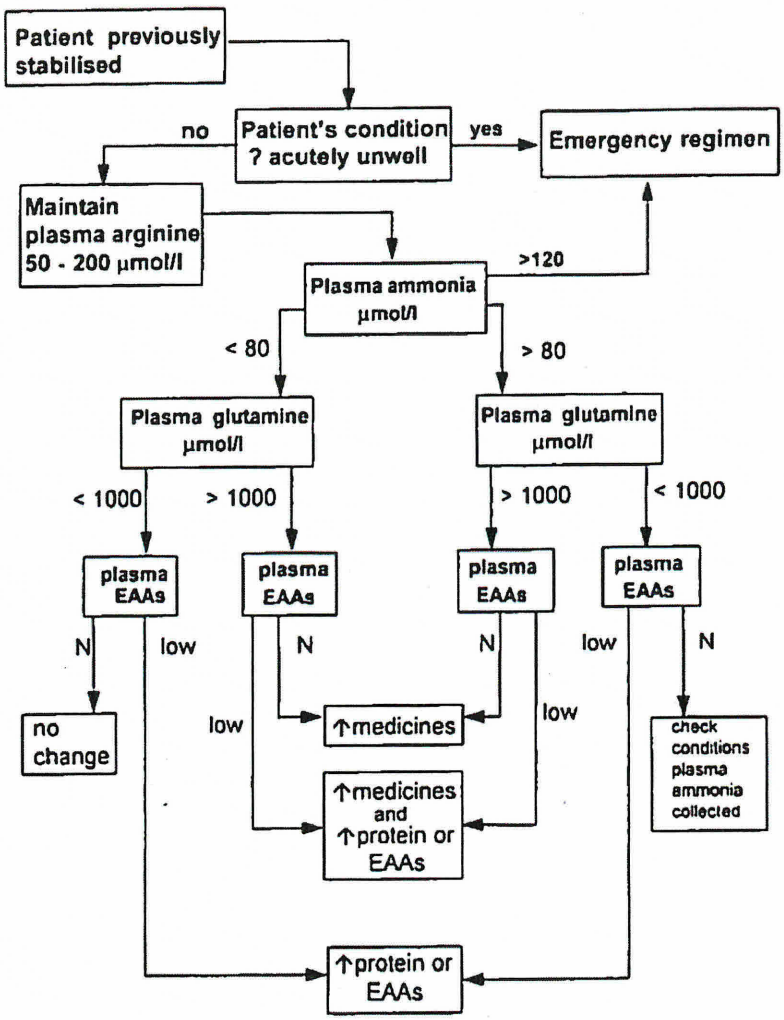

Fig. 17.2. Guidelines for the management of patients with urea-cycle disorders (except arginase deficiency). This is intended for use in patients who have been stabilised previously and should only be regarded as a guide, as some patients may have individual requirements. For more detail and information about doses, please refer to the text. *EAAs*, essential amino acids

reflects not only the residual enzyme activity but also many other factors, including appetite and growth rate. Some patients have an aversion to protein, so it can be difficult to get them to take even their recommended intake. Consequently, they are likely to need smaller doses of sodium benzoate and phenylbutyrate. Others prefer to take more protein, and this has to be balanced by an increase in the dosages of benzoate and phenylbutyrate. Some will not take adequate quantities of sodium benzoate or sodium phenylbutyrate and, therefore, their protein intakes necessarily have to be stricter than would be needed if they took the medicines. Hence, for each patient, a balance must be found between their protein intake and the dose of their medicines to achieve good metabolic control.

Assessment for Treatment

All patients with urea cycle disorders are at risk of acute decompensation with acute hyperammonaemia. This can be precipitated by different kinds of metabolic stress, such as fasting, a large protein load, infection, anaesthesia or surgery. For this reason, all patients should have detailed instructions of what to do when they are at risk. We routinely use a three-stage procedure [24]. If the patient is off-colour, the protein is reduced, and more carbohydrate is given. If symptoms continue, protein should be stopped and a high-energy intake given with their medication by day and night. However, if they cannot tolerate oral drinks and medicines, are vomiting or are becoming progressively encephalopathic, they should go to a hospital for assessment and intravenous therapy without delay. For further practical details, see Dixon and Leonard [24]. Patients should also have a high carbohydrate intake before any anaesthesia or surgery.

For patients who are seriously ill with hyperammonaemia, treatment is urgent. The steps are listed below, and early treatment is essential (Chap. 3).

Emergency Treatment

The volumes which are given are related to age and the condition of the patient. Fluid volumes should be

restricted if there is any concern about cerebral oedema.

- Stop protein intake.
- Give a high energy intake.
  1. Orally: (a) 10–20% soluble glucose polymer or (b) protein-free formula or
  2. Intravenously: (a) 10% glucose by peripheral infusion or (b) 10–25% glucose by central venous line
- Give sodium benzoate up to 500 mg/kg/day orally or intravenously.
- Give sodium phenylbutyrate up to 600 mg/kg/day.
- Give L-arginine:
  - Up to 700 mg/kg/day in citrullinaemia and arginosuccinic aciduria.
  - Up to 150 mg/kg/day in OTC and CPS deficiencies.
  - For the emergency treatment of hyperammonaemia before diagnosis is known, this may be replaced by L-arginine 300 mg/kg/24 h and L-carnitine 200 mg/kg/24 h. Both can be given orally or intravenously.
- Dialysis. If hyperammonaemia is not controlled or the medicines are not immediately available, haemofiltration (or haemodialysis/haemodiafiltration) should be started without delay. Alternatively, peritoneal dialysis can be used, but this is a less effective method for reducing hyperammonaemia.
- Treat other conditions (sepsis, fits, etc.).
- Monitor intracranial pressure with the usual measures to reduce raised pressure and maintain perfusion pressure.

Prognosis

The prognosis in these disorders is closely related to the age of the patient and their condition at the time of diagnosis. For those patients who present with symptomatic hyperammonaemia in the newborn period, the outlook is very poor. Even with the most aggressive treatment, the majority of the survivors will be handicapped. Those who are treated prospectively do better, but there may still be significant complications [25]. For these patients, there remains a serious risk of decompensation, and careful consideration should be given to early liver transplantation, which may offer the hope of a better long-term outlook [26]. Of those who present later, their neurological problems at the time of diagnosis are critical, as most will have already suffered neurological damage. At best, this may apparently resolve, but almost all are left with some degree of learning and neurological problems. Patients who have widespread cerebral oedema almost all die or survive with severe handicaps. By contrast, those who are treated prospectively have a better outcome.

Genetics and Prenatal Diagnosis

The genes for urea-cycle enzymes (except *N*-acetylglutamate synthetase) have been mapped, isolated and fully characterised [27]. Many mutations have been described. The most common urea cycle disorder is OTC deficiency, which is an X-linked disorder in which molecular genetic studies are particularly helpful. When the diagnosis of OTC deficiency is established, it is necessary to take a careful family history and for the mother's carrier status to be assessed. Currently, if the mutation is not known, the most convenient investigation is the allopurinol test, which is used to detect increased de novo synthesis of pyrimidines (see "Metabolic Derangement"). It appears to have good sensitivity and specificity [28, 29]. This is easier than the protein- or alanine-loading tests and carries no risk of hyperammonaemia. Prenatal diagnosis using a gene probe for mutation detection or to identify informative polymorphisms can help most families. However, whilst the phenotype of the males can be predicted, that of the females cannot because of the random inactivation of the X chromosome. This presents a problem when counselling families, but the prognosis for females who are treated prospectively from birth is good.

All the other conditions have autosomal-recessive inheritance, and prenatal diagnosis is possible for all disorders except *N*-acetyl glutamate synthetase deficiency. For CPS deficiency, prenatal diagnosis using closely linked gene markers is now possible for a substantial proportion of families. If the molecular-genetic studies are uninformative, prenatal liver biopsy is a possible alternative. Citrullinaemia and argininosuccinic aciduria can both be diagnosed on chorionic villus biopsy. Arginase deficiency can be diagnosed either with molecular-genetic studies or, if they are not informative, with a foetal blood sample.

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