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REVIEW ARTICLE

Diagnosis and treatment of urea cycle disorders

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Abstract:
Urea cycle disorders (UCDs) comprise a group of inherited defects of metabolism affecting the detoxification of excess nitrogen and, hereby, leading to hyperammonemia. The urea cycle consists of six consecutive enzymatic steps and is located both in the mitochondria and cytosol of periportal hepatocytes. In addition, two transporters are required for the urea cycle function. Besides the detoxification of excess nitrogen, the endogenous synthesis of the amino acid arginine is the second role of the urea cycle.
The clinical presentation of UCDs comprises a continuum ranging from early onset hyperammonemic decompensation in severe defects to late onset presentation in less severe affected patients at any age. Since ammonia is primarily toxic to the central nervous system, signs and symptoms of UCDs are mainly neurological but, unfortunately, highly unspecific. Therefore, it can be challenging to clinically diagnose patients suffering from UCDs. If a UCD is suspected, ammonia should be measured immediately. To confirm the diagnosis, a variety of biochemical, enzymatic and genetic tools exist.
Most UCD patients need a strict treatment protocol consisting of dietary protein restriction, nitrogen scavenger drugs, and vitamin and amino acid supplementations. Treatment must be followed lifelong unless liver transplantation is performed.
Patients with UCDs are still affected by a poor outcome quoad vitam et sanitam. To improve both survival rates as well as the quality of life in surviving patients will largely depend on an increased awareness of all medical professionals towards this group of inherited metabolic defects.
Keywords: *hyperammonemia, nitrogen metabolism, inherited metabolic defect, changed consciousness, cerebral edema*
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Introduction

Accumulation of excess nitrogen leads to hyperammonemia and neurological sequelae if ammonia is not sufficiently detoxified. Detoxification of excess nitrogen depends largely on the habitat. While aquatic animals (ammoniotelic animals) excrete nitrogen as ammonia and reptiles (uricotelic animals) as uric acid, respectively, terrestrial animals and humans (ureotelic organisms) can excrete excess nitrogen only as urea. In the mammalian organism, the urea cycle is the only pathway capable of detoxification of excess nitrogen. The urea cycle is fully expressed only in periportal hepatocytes but in part also in small intestine and kidney.

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Urea cycle disorders (UCDs) comprise a group of inherited defects of metabolism affecting the detoxification of excess nitrogen and, hereby, leading to hyperammonemia. The urea cycle consists of six consecutive enzymatic steps of which each three are located in the mitochondrion (N-acetylglutamate synthase, NAGS; Carbamoylphosphate synthetase 1, CPS1; Ornithine carbamoyltransferase, OTC) and in the cytosol (Argininosuccinate synthetase, ASS; Argininosuccinate lyase, ASL; Arginase 1, ARG1), respectively (1). In addition, two transporters, namely ORNT1 (if defect, leading to hyperornithinemia-hyperammonemia-homocitrullinuria [HHH] syndrome)

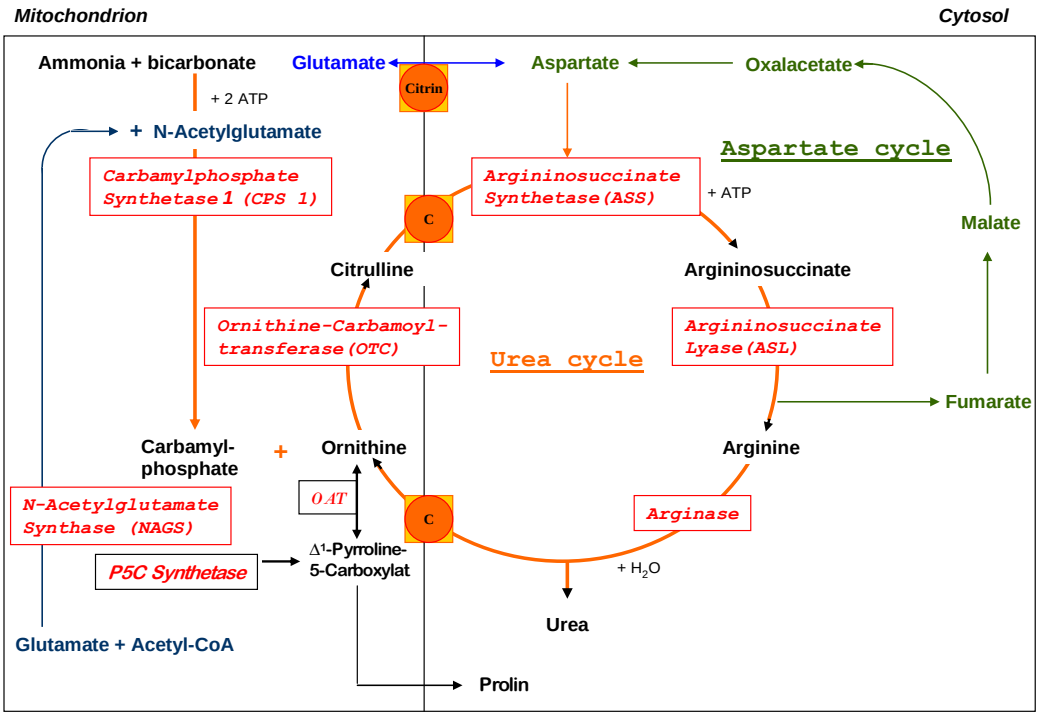

Figure 1: The urea cycle and related metabolic pathways

Enzymes are depicted in red and italics. C: carrier = transporter between cytosol and mitochondrion, if defect, hyperammonemia-hyperornithinemia-homocitrullinuria (HHH)-syndrome results; OAT: ornithine aminotransferase; P5C synthetase: pyrroline-5-carboxylate synthetase.

Table 1: Disorders of the urea cycle

Disorder	Name of enzyme / transporter	OMIM number	Gene	Location
NAGS deficiency	N-acetylglutamate synthase	237310	NAGS	17q21.31
CPS1 deficiency	Carbamoylphosphate synthetase 1	237300	CPS1	2p35
OTC deficiency	Ornithine carbamoyltransferase	311250	OTC	Xp21.1
ASS deficiency = citrullinemia type 1 = classic citrullinemia	Argininosuccinate synthetase	215700	ASS1	9q34.1
ASL deficiency = argininosuccinic aciduria	Argininosuccinate lyase	207900	ASL	7cen-q11.2
ARG1 deficiency = hyperargininemia	Arginase 1	207800	ARG1	6q23
HHH syndrome = hyperornithinemia-hyperammonemia-homocitrullinuria syndrome	Mitochondrial ornithine transporter ORNT1	238970	SLC25A15	13q14
Citrullinemia type 2	Citrin = aspartate/glutamate carrier	603471 605814	SLC25A13	7q21.3

OMIM: Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim/).

and Citrin (if defect, leading to citrullinemia type 2), respectively, which are both located at the inner mitochondrial membrane, are required for the urea cycle function (2-5) (Table 1).

Besides the detoxification of excess nitrogen, the endogenous synthesis of the amino acid arginine is the second role of the urea cycle. In defects of the urea cycle apart from ARG1 deficiency, arginine becomes an essential amino acid (Figure 1).

The clinical presentation of UCDs can vary considerably and is best described as a continuum ranging from early onset hyperammonemic decompensation during the first days of life in severe defects to a late onset presentation in less severe affected patients at any age (6). Since ammonia is toxic primarily to the central nervous system, signs and symptoms of UCDs are mainly neurological but, unfortunately, highly unspecific (7). Therefore, it can be challenging to clinically diagnose patients suffering from UCDs. The single most important factor that influences the prognosis of affected patients is probably to think of UCDs early enough to prevent neurological consequences of hyperammonemia. If a UCD is suspected, ammonia should be measured immediately. To confirm the diagnosis, a variety of biochemical, enzymatic and genetic tools exist.

UCDs can currently not be cured unless liver transplantation is performed. Since liver transplantation has a number of own limitations it is not yet widely applied but should always be considered in severely affected patients (8). At the moment, most UCD patients need a strict treatment protocol consisting of dietary protein restriction, nitrogen scavenger drugs, and vitamin and amino acid supplementations. This treatment must be followed lifelong.

Patients with a complete enzyme deficiency, particularly those with intramitochondrial defects of the urea cycle, will most likely present already during the first days of life and carry a high risk of fatal hyperammonemia with mortality rates up to 50% despite early and aggressive treatment (9, 10). Likewise, patients with late onset presentations still carry a high risk of a fatal outcome of their first hyperammonemic decompensation but are usually less severe affected (10). Taken together, patients with UCDs are still affected by a poor outcome *quoad vitam et sanitam*. To improve both survival rates as well as the quality of life in surviving patients will largely depend on an increased awareness of all medical professionals towards this group of inherited metabolic defects.

Diagnosis of urea cycle disorders

Clinical diagnosis and differential diagnosis

Symptoms of patients suffering from UCDs are mostly related to hyperammonemia and are mainly neurological. The age of the patient is less important with respect to the clinical phenotype because signs and symptoms are unspecific in all age groups (6). However, the type of presentation can be acute or chronic and this is of clinical importance.

In acute hyperammonemia impairment of consciousness is the leading sign ranging from mild lethargy to deep coma. In addition, hyperammonemia induced cerebral edema can lead to vomiting and seizures. In rare instances, patients present with acute liver failure or multiorgan failure (11). In neonatal patients the clinical picture resembles sepsis or respiratory distress and these are the differential diagnoses that are initially suspected in most patients sometimes leading to dramatic delays in correct diagnosis (10).

In chronic presentation, impairment of consciousness is also leading sign but is rather characterized by confusion, lethargy, dizziness, migraine-like headaches in addition to other neurological signs such as tremor, dysarthria or ataxia. In many patients, protein aversion leads to a self-chosen vegetarian diet. Moreover, symptoms in patients with chronic hyperammonemia can resemble psychiatric disorders or can lead to learning disabilities and mental retardation (12). Sometimes, there is an episodic character of signs and symptoms of chronic hyperammonemia (13).

It is important to note, that the variability of the clinical phenotype of UCDs is very broad even within one family (14). This is particularly true in X-linked OTC deficiency, a disorder that can lead to mild as well as severe metabolic decompensations in both sexes (15, 16).

All situations in which the nitrogen detoxifying

Table 2: Most relevant metabolic differential diagnosis of hyperammonemia		
Disorder	**Key metabolite**	**Key tests**
Urea cycle disorders	Glutamine, citrulline, arginine orotic acid	Amino acids in plasma, orotic acid in urine
Organic acidurias	Methylmalonic acid, methylcitrate, propionic acid, isovaleric acid	Organic acids in urine
Fatty acid oxidation defects and carnitine cycle defects	Acylcarnitines	Acylcarnitine profile in plasma or dried blood spot
Hyperinsulinism-hyperammonemia syndrome = Glutamate dehydrogenase (GLDH) defect	Glucose	Glucose and insulin in serum
Lysinuric protein intolerance	Lysine, citrulline, arginine, ornithine	Amino acids in urine
Transient hyperammonemia of the newborn	Glutamine (low despite hyperammonemia)	Amino acids in plasma, none specific

capacity of the urea cycle is exceeded may lead to hyperammonemia. This can be the result of an excess in exogenous protein intake but also if endogenous protein catabolism is increased. The latter may occur in any intercurrent viral illness or fever of any cause but also in case of poor nutritional energy intake or rapid weight loss. In addition, iatrogenic causes such as high dose glucocorticoids or fasting around surgery are possible triggers of metabolic decompensations in UCDs (17, 18).

The clinical picture of UCDs can resemble those of many other inborn errors of metabolism. This is particularly the case in neonatal presentations of organic acidemias and fatty acid oxidation defects (Table 2).

In few patients with UCDs, acute liver failure has been the presenting sign (11). Likewise, coagulation disturbances are frequently found in patients with HHH-syndrome (19).

Biochemical diagnosis of UCDs

Measurement of plasma ammonia is the single most important laboratory test to detect UCDs. However, hyperammonemia is unspecific and must be regarded as surrogate marker for an insufficient detoxification of excess nitrogen. In the acutely ill newborn, absence of hyperammonemia makes the diagnosis of UCD very unlikely but outside the newborn period hyperammonemia does not always exist in UCDs. Ammonia measurement requires some preanalytical precautions to avoid false high ammonia concentrations (20).

Next to ammonia measurement, careful interpretation of plasma amino acid profiles is essential (21). There exist some specific changes to the amino acid profile, such as marked elevation of citrulline in citrullinemia type I which is less marked in ASL deficiency. Likewise, presence of argininosuccinate is a finding specific for ASL deficiency which allows the direct diagnosis of this specific UCD directly from the amino acid profile. This is, unfortunately, not the case in the mitochondrial UCDs where low levels of plasma citrulline are rather suggestive than diagnostic. However, for the single most common UCD, OTC deficiency, presence of elevated urine orotic acid or orotidine can be a helpful diagnostic tool (Table 3).

In about half of the patients with acute presentations of UCDs, respiratory alkalosis can be found (10). This might help to discriminate in case of an acutely ill newborn thought to suffer from sepsis where metabolic acidosis but not respiratory alkalosis can be expected. Presence of respiratory alkalosis should in any case alert neonatologists and should prompt immediate ammonia measurement.

Enzymatic testing in UCDs

Since biochemical parameters do not always allow a definitive diagnosis in UCDs, enzymatic testing may be required to confirm the diagnosis.

Table 3: Diagnostics of urea cycle defects

Disorder	Characteristic metabolites	Confirmation
NAGS deficiency	Low citrulline in plasma, low / absent orotic acid in urine	Genetic analysis or enzyme analysis in liver
CPS1 deficiency	Low citrulline in plasma, low / absent orotic acid in urine	Genetic analysis or enzyme analysis in liver
OTC deficiency	Low citrulline in plasma, elevated orotic acid in urine	Genetic analysis
ASS deficiency = citrullinemia type 1 = classic citrullinemia	Elevated citrulline in plasma	Genetic analysis
ASL deficiency = argininosuccinic aciduria	Argininosuccinic acid in plasma or urine presence of which is already diagnostic	Enzyme analysis in red blood cells or genetic analysis
ARG1 deficiency = hyperargininemia	Elevated arginine in plasma	Enzyme analysis in red blood cells or genetic analysis
HHH syndrome = hyperornithinemia-hyperammonemia-homocitrullinuria syndrome	Homocitrulline in urine	Genetic analysis
Citrullinemia type 2	Elevated citrulline, arginine, methionine, threonine, tyrosine, lysine in plasma	Genetic analysis

In general, enzyme testing can be used for confirmation in all UCDs but techniques vary between the single disorders and sometimes require invasive sampling (22). For instance, enzyme assays for the mitochondrial UCDs require a liver biopsy. In contrast, for investigations of ASL and ARG1 deficiencies, enzyme activities in red blood cells can be measured. The role of enzyme analysis for the confirmation of UCDs has dwindled mainly due to the invasiveness of some of the tests and also due to the additional advantage of the feasibility of prenatal testing in future pregnancies if mutation analysis is applied. However, enzyme testing is still helpful in some situations, for instance to fast distinguish between deficiencies of NAGS and CPS1, respectively. Finally, it is important to note that a low protein diet can lead to false low activities of UCD enzymes. In addition, preanalytical careful management of a liver biopsy sample including rapid freezing, transport on ice, and avoiding repetitive thawing, is a prerequisite for a correct result, particularly if instable enzymes, such as CPS1, are to be investigated.

Genetic testing for UCDs

Genetic testing is feasible in all UCDs and is mostly done by PCR and direct sequencing of DNA samples. The only exception to that is CPS1 deficiency, in which some laboratories currently prefer an RNA based approach due to the size of the *CPS1* gene (23). In practice, mutation analysis for OTC deficiency as the most common UCD is offered by many laboratories while genetic investigations for all other UCDs is only performed in single specialized institutions.

Mutation analysis can be regarded as method of choice for a definite diagnosis in UCDs in which metabolite profiles are not diagnostic and enzymatic testing would be invasive. In addition, mutation analysis should be done in all situations in which later prenatal testing might be required. Furthermore, it is method of choice to get a diagnosis in deceased patients in whom only DNA is available for further investigations.

In general, mutation analysis will allow a diagnosis in most patients. As an exception to this, the reported detection rate in DNA based OTC mutation analysis is only about 80% (24). This is in part probably due to the large intronic sequences in the *OTC* gene. In the meanwhile, alternative methods have been described to overcome this problem (25, 26). In the future, other techniques such as next generation sequencing might become available allowing for a fast, inexpensive and comprehensive study of UCD genes.

Prenatal testing

In all UCDs, prenatal testing is feasible and also often requested in families previously affected by a deceased index-patient. Therefore, there is a need for an early, fast and safe method to detect affected fetuses. Nowadays, this can be best achieved by applying genetic means if the mutation in the index patient is known. Prenatal mutation analysis requires chorionic villi sampling for DNA isolation. Then, direct mutation analysis, together which exclusion of maternal contamination, is a straightforward approach and has been reported in all UCDs (27).

If the mutation in the index patient is not known, biochemical methods can be applied for defects of ASS and ASL where measurement of citrulline and argininosuccinate in amniotic fluid, respectively, can serve as specific parameters (28). In addition, enzyme tests using cultured chorionic villus cells or cultured amniotic fluid cells can be done for deficiencies of ASS and ASL, respectively (29).

In NAGS deficiency, carbamylglutamate as a licensed drug allows effective treatment leading to good outcome in affected patients (30). Therefore, the situation with respect to prenatal testing is different from all other UCDs and the availability of an effective treatment should influence the prenatal management.

Therapy

Patients suffering from UCDs require a lifelong treatment as soon as the diagnosis has been made. The only exceptions to this are patients with very mild variant forms which are described for most UCDs and also patients who received a liver transplantation. Therapy of UCDs comprises always a combination of diet, medications and substitution of essential amino acids and vitamins. Despite treatment, patients have a high risk of metabolic decompensations with acute hyperammonemia. In this situation, the treatment plan must be changed immediately and measures to fight acute hyperammonemia have to be started without any delay.

Dietary treatment of UCDs

Most patients with UCDs will need to be treated with a protein restricted diet allowing only for the minimum daily intake of natural protein (31, 32). In practice, this can often only be achieved by a strict vegetarian diet plus the use of industrial substitutes for many foods. Dietary protein restriction aims for avoiding excess of nitrogen but, at the same time, carries the risk of dietary overrestriction leading to malnutrition, essential amino acids deficiencies, and impaired growth (33). Therefore, it can be very challenging to keep the balance between excess nitrogen intake and overrestriction in patients on a low protein diet. Also, dietary treatment needs re-evaluation at regular intervals particularly during infancy and childhood when recommended ranges of protein intake are subject of great variation.

In most patients with dietary protein restriction, supplementation of essential amino acids is required to avoid their deficiencies. This is particularly relevant for the branched chain amino acids valine, isoleucine and leucine which have been shown to be regularly depleted in UCD patients (34, 35). To achieve sufficient supplementation, synthetic amino acid mixtures containing essential amino acids should be part of any nutritional regime in UCD patients. Likewise, vitamin intake can be impaired in low protein diet resulting in a need for also vitamin supplementation.

Dietary treatment of UCDs aims primarily at maintenance of anabolism which is a prerequisite for the avoidance of endogenous protein degradation. Therefore, also deficiency of calories intake must be avoided in UCD patients at any age. This is certainly best achieved by following recommended ranges of daily calories intake.

Even in severe defects of urea cycle enzymes, the metabolic control is often easy to achieve during the first year of life. If growth slows down, the risk of catabolism is much increased often resulting in pronounced metabolic instability. Then, frequent adjustments of the dietary regime are often necessary as is close monitoring of the patient's thriving and biochemical parameters.

Nitrogen scavenging drugs

Nitrogen scavenging drugs comprise a group of currently only two substances which allow for alternative excretion of excess nitrogen bypassing the urea cycle (6, 36). The exploitation of alternative pathways for excess nitrogen detoxification is important for the management of acute episodes of hyperammonemia but also part of long term therapy

of UCD patients. Sodium benzoate and sodium phenylbutyrate exert their beneficial effect on excess nitrogen removal by conjugating with glycine and glutamine, respectively, allowing for direct urinary excretion of hippurate and phenylacetylglutamine, respectively. The use of nitrogen scavengers for treatment of acute neonatal decompensations has been shown to improve mortality, however, to some extent at the cost of an increased neurological morbidity (37).

Sodium benzoate can be given either orally or intravenously. Sodium phenylbutyrate can only administered orally but instead, its metabolite sodium phenylacetate can be given intravenously. While sodium benzoate is available only as a chemical agent, sodium phenylbutyrate is available as a licensed drug in many countries. For both substances there are many years of experience for the use in acute and chronic therapy. If given orally, both sodium benzoate and sodium phenylbutyrate should be divided into three or four daily doses to optimize the nitrogen scavenging effect.

Treatment with sodium phenylbutyrate can result in deficiencies of branched chain amino acids (34, 35). The reason for this is the phenylbutyrate-induced depletion of glutamine which leads to increased transamination of branched chain amino acids. Therefore, amino acid profiles of UCD patients on sodium phenylbutyrate need to be followed with particular caution.

Arginine and citrulline

Arginine and citrulline which are both intermediary metabolites of the urea cycle are used in UCD patients for the following two reasons: arginine becomes an essential amino acid in all UCDs apart from ARG1 deficiency (33). To avoid arginine deficiency, supplementation of arginine is performed in most patients. As an alternative, citrulline can be used if the defect lies proximal to the enzyme ASS (38). The second reason to supplement arginine or citrulline is to use these amino acids as a vehicle for excess nitrogen excretion in urine. This is achieved by establishing the residual function of the part of the urea cycle which is still intact resulting in the urinary excretion of citrulline and/or argininosuccinate. In patients affected with mild variants of ASS or ASL deficiency, supplementation of arginine, with or without dietary protein restriction, may be sufficient to maintain metabolic control. Arginine and citrulline should to be divided in three or four daily doses to optimize their efficacy (38).

Use of gastrostomy tubes in patients with UCDs

Given the importance of a strict dietary protocol ensuring maintenance of calories intake and essential amino acid supplementation as well as the need for multiple daily doses of various medications, use of a gastrostomy tube might be a relief for patients and families (32, 39). Many of the medications are unpalatable and, thus, their regular intake might not be easy to achieve. In addition, a gastrostomy tube might be helpful in avoiding or managing acute metabolic decompensations because the appropriate administration of calories, essential amino acids and medications will be facilitated particularly in infants and children during illness. Thus, using gastrostomy tubes may even help to decrease the number of days in hospital.

Emergency protocols for UCD patients

It is of utmost importance for all UCD patients to have an up-to-date written emergency protocol that explains all aspects of care including diet and medications. Likewise, a detailed plan describing the essential measures in case of an emergency should be provided to avoid any delay. This emergency plan should be explained not only to the family but also to health care facilities involved, namely the local emergency room, and to any other person with a regular contact to the patient such as school teachers.

Long term therapy

Long term therapy of UCDs relies on a combination of dietary protein restriction, administration of nitrogen scavenging drugs, and supplementation of essential amino acids and vitamins (32, 35, 38). While patients with severe defects of any UCD enzyme will in general need to be treated with all three modalities, patients with variant forms of UCDs might not need all treatment options. In this respect, treatment of UCDs is always very much individualized.

Treatment of acute episodes

Acute hyperammonemia is always an emergency situation (9, 10, 40). It requires the immediate withdrawal of exogenous protein sources as well as the start of high caloric intake which is best achieved by intravenous glucose (with or without insulin). The

aim is to reverse endogenous protein catabolism as fast as possible to avoid ongoing protein breakdown and further accumulation of waste nitrogen (41).

The elimination of exogenous protein will, however, not suffice to treat acute hyperammonemia if it is not combined with infusions of high doses of glucose. Also, stop of protein intake may lead to deficiencies of essential amino acids which can result in continuing endogenous protein breakdown. Therefore, exogenous protein sources should not be eliminated longer than 24 to 48 hours. After that time, at least essential amino acids must be reinstituted (42).

In acute hyperammonemia, high caloric intake is best achieved by intravenous solutions with glucose 10%. Often, higher concentrations of glucose are necessary and might require the concomitant use of insulin which might be in addition beneficial because of its anabolic effect. This might also lead to the need for central venous lines. A central venous line should always be considered if a patient needs parenteral nutrition with high concentrations of glucose for more than one or two days. Central venous lines will also facilitate fluid management during acute episodes of hyperammonemia as well as the continuous supply of nitrogen scavenging drugs and arginine.

Careful fluid management during acute hyperammonemia is critical since sufficient urine production is a prerequisite for the excretion of metabolic waste products. At the same time, if hyperammonemia has already led to an increase in intracranial pressure, a further fluid overload should be avoided.

Liver transplantation

Liver transplantation has been performed in most urea cycle disorders (8, 43). The total numbers are still small but in patients with OTC deficiency, there are reports on more than 40 liver transplantations until 2010. The overall survival rate of UCD patients after liver transplantation is the same as in patients transplanted for other indications. Liver transplantation does lead to a rapid normalisation of the metabolic situation allowing for a stop of alternative pathway therapy as well as stop of dietary protein restriction. In most cases orthotopic liver transplantation has been performed using cadaveric organs. Advanced surgical techniques now allow transplanting infants of 3 to 6 months with similar outcomes than those in older children. With respect to the neurological outcome, liver transplantation is a therapeutical alternative in patients affected by severe neonatal hyperammonemia or if recurrent metabolic decompensations are threatening the neurological development.

Hepatocyte transplantation

Hepatocyte transplantation is a recently described therapeutical option which is intended to bridge a patient with severe neonatal hyperammonemic decompensation until liver transplantation can be performed (44, 45). Up till now, it was only performed in single patients and many aspects of this treatment modality, such as the technique of vascular access applied or the number of cells necessary for a successful transplantation, are currently evaluated to define the efficacy of this new treatment modality.

Summary

UCDs are by no means rare disorders with only relevance for specialized neonatologists or metabolic physicians. Rather, on the basis of their frequent presentation outside the neonatal period, the relatively high incidence of the most common UCD, OTC deficiency, and of the dramatic consequences of delayed diagnosis of acute hyperammonemia, an increased awareness of all medical professionals towards this group of disorders is urgently needed and would be beneficial with respect to the outcome of the patients. In practice, in all unexplained changes in consciousness, hyperammonemia should be excluded. To later confirm the diagnosis of a UCD, specific metabolic, enzymatic or genetic testing is required. Treatment comprises a combination of dietary protein restriction, medications, and supplementation of vitamins and essential amino acids and can be very challenging in all age groups.

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