EIMD

European registry and network for
Intoxication type Metabolic Diseases

For healthcare professionals

Urea Cycle Disorders

www.e-imd.org

Abstract

Urea cycle disorders (UCDs) comprise a group of inborn errors of metabolism affecting the detoxification of ammonia. The urea cycle consists of six consecutive enzymatic steps and in addition, two transporters are required for the urea cycle function. The urea cycle is present in the liver and is located in mitochondria as well as in the cytosol of only periportal hepatocytes. If any of these enzymes or transporters is defect, the main resulting medical problem is hyperammonemia which can be life-threatening. Besides the detoxification of ammonia, the synthesis of the amino acid arginine is another important function of the urea cycle.

The clinical phenotypes of patients affected by UCDs comprise a continuum ranging from early onset (i.e. neonatal during the first days of life) hyperammonemic crisis in severe defects to late onset of disease in less severely affected patients which can occur at any age (including late adulthood). If hyperammonemia develops, signs and symptoms are mainly neurological because ammonia is primarily toxic to the central nervous system; however, the clinical picture is unfortunately highly unspecific. Thus, to diagnose patients suffering from UCDs on their clinical presentation alone will be challenging. For this reason, ammonia must be determined immediately in any situation when a UCD is suspected.

If a UCD is suspected, a number of biochemical, enzymatic and genetic tools exist. To contact a specialist might be a good idea to plan the work-up most efficiently and least invasive. For some UCDs, biochemical tests alone can be sufficient to make the diagnosis. Others require either enzymatic or genetic tests. For reasons of family investigations and future pregnancies, mutation analysis should be considered in all affected patients.

Most UCD patients need to follow a strict treatment regime with dietary protein restriction, sufficient energy intake, supplementation of essential amino acids,

minerals and micronutrients, and drugs for alternative ammonia detoxification. To date, liver transplantation is the only cure of a UCD. Strict adherence to treatment is necessary lifelong unless liver transplantation has been done.

Patients with UCDs have a limited prognosis regarding survival and quality of life. To improve survival rates as well as the quality of life in those surviving a metabolic decompensation requires early detection before onset of irreversible brain damage and thus increased awareness of healthcare professionals towards this group of inborn errors of metabolism.

Disease name + OMIM number + Synonyms

The following table lists the disease names of UCDs, commonly used synonyms and the respective OMIM numbers.

Disease name	Synonyms	OMIM #
NAGS deficiency	-	237310
CPS1 deficiency	-	237300
OTC deficiency	OCT deficiency	311250
ASS deficiency	citrullinemia type 1, classic citrullinemia	215700
ASL deficiency	argininosuccinic aciduria, ASuria	207900
ARG1 deficiency	hyperargininemia	207800
HHH syndrome	hyperornithinemia-hyperammonemia-homocitrullinuria syndrome	238970
Citrin deficiency	citrullinemia type 2	603471, 605814

Disease definition in summary

UCDs comprise a group of inborn errors of metabolism in which a defect in ammonia detoxification leads to hyperammonemia. Patients can be affected at any time in life and the disorders can be life-threatening. The main problem

concerns the toxic effect of hyperammonemia on brain function during metabolic decompensations.

Epidemiology

The exact prevalence of UCDs is not known. Published numbers from single centers have to be considered as estimations. Accordingly, there are no firm data on carrier frequencies. The following numbers have been published:

- NAGS deficiency: very rare, no numbers published
- CPS1 deficiency: 1:62.000
- OTC deficiency: 1:14.000
- ASS deficiency: 1:57.000
- ASL deficiency: 1:70.000
- ARG1 deficiency: 1:350.000
- HHH syndrome: very rare, no numbers published
- Citrin deficiency: 1:21.000 in Japan, in other parts of the world very rare (this disease is not enclosed in E-IMD)

Etiology

The following table lists the names of enzymes and transporters, their corresponding gene names, the gene map locus, and EC numbers of affected enzymes.

Name of enzyme /transporter	Gene	Location	EC numbers
N-acetylglutamate synthase	NAGS	17q21.31	2.3.1.1
Carbamoylphosphate synthetase 1	CPS1	2p35	6.3.4.16
Ornithine transcarbamylase	OTC	Xp21.1	6.3.4.16
Argininosuccinate synthetase	ASS	9q34.1	6.3.4.16
Argininosuccinate lyase	ASL	7cen-q11.2	4.3.2.1
Arginase 1	ARG1	6q23	3.5.3.1
Mitochondrial ornithine transporter ORNT1	SLC25A15	13q14	-
Citrin = aspartate/glutamate carrier	SLC25A13	7q21.3	-

Clinical presentation

- Age at onset of first symptoms can be at any age. A large proportion of patients already present very early after birth on day 2 or 3 of life. However, manifestation (= onset of first symptoms) is after the neonatal period (= first 28 days of life) for up to 50% of patients and can be triggered by any catabolic situation. Typical risk factors are: slowed growth at end of infancy, infections, and prolonged fasting.
- Major acute symptoms and long-term organ complications mainly affect the central nervous system and can often be summarised as “change in consciousness”. Acute symptoms can range from subtle neurological changes (lethargy, headaches, tremor, changed personality or other psychiatric symptoms) to subacute loss of vision, seizures or coma. Long-term complications are dependent on the number and degree of metabolic decompensations and comprise often (severe) psychomotor retardation.
- Disease variants are known for all UCDs. Some patients have an unusual mild clinical course or are even asymptomatic (after being diagnosed through newborn screening or through family investigations). Other patients present with unusual symptoms mimicking other diseases.

- Asymptomatic cases are also known for all UCDs and often detected in newborn screening or through family screening. Most asymptomatic UCD patients are female OTC carriers (identified through family screening) who have remained asymptomatic so far but may show biochemical changes with yet uncertain clinical relevance. Other examples are patients with mild forms of citrullinemia type 1 or argininosuccinic aciduria (often identified through newborn screening) showing seemingly an only biochemical phenotype. Open questions concern the problem whether or how to identify them and how to decide who should be treated or not.

Diagnostic methods

- Basic metabolic tests are suited to raise the suspicion of a UCD. The most important parameter is plasma ammonia which is always elevated during metabolic decompensations of UCDs. Other basic test such as blood gases, serum glucose, lactate, or ketone bodies are not suited to diagnose UCDs.

- Metabolite analysis is required to further investigate any suspicion of a UCD. Here, the determination of plasma amino acids is the single most important test because it can reliably identify some UCDs (e.g. citrullinemia and argininosuccinic aciduria). However, in undiagnosed patients with a suspicion of a UCD, urine organic acids and blood acylcarnitines should always be investigated in parallel because these tests address the most common differential diagnoses of UCDs, namely organic aciduria and fatty acid oxidation defects, respectively. Determination of urine orotic acid and orotidine can help to establish the diagnosis of the most common UCD, OTC deficiency.

- Enzyme analysis can be done for most UCDs using liver tissue; for some UCDs, other tissues (e.g. red blood cells, cultured fibroblasts) can be used instead. Unfortunately, enzyme analysis has only limited value in

the diagnosis of OTC deficiency because this disorder is X-linked and heterozygous female patients may have a mosaic distribution of mutant enzyme activity in liver.

- Mutation analysis is available for all UCDs. In most cases, mutation analysis can be done using DNA from normal blood sampling. An exception to this is CPS1 deficiency for which some labs prefer starting with RNA-based studies. Because mutation analysis offers the additional advantages of prenatal testing for later pregnancies and is prerequisite for family investigations, it is now recommended as the method of choice if confirmation is needed.

Differential diagnosis

- Other diseases with overlapping clinical presentation are best described in an age dependent way. In newborns, septicemia can lead to a similar clinical presentation and is by far more common than UCDs. It should be stressed that the diagnosis of a UCD should be considered in any newborn with “septicemia” but lacking common risk factors, in the absence of typical lab signs for an infection, and if there is no improvement after start of antibiotic treatment. In patients outside the newborn period, UCDs can mimic many neurological disorders including infections (e.g. encephalitis), epilepsy, psychiatric disorders, and intoxications.

- Other diseases with overlapping biochemical abnormalities are best differentiated by the above mentioned metabolic tests (urine organic acids and orotic acid, blood acylcarnitines). Besides, there are only few other conditions (e.g. mitochondrial disorders) that may lead to similar biochemical alterations. Diagnostic pitfalls can occur in patients with mild courses of UCDs which might be missed outside catabolic states. Therefore, metabolite analysis should be repeated during a catabolic situation to increase the sensitivity of the tests applied.

Antenatal diagnosis and genetic counseling

Prenatal testing is feasible in all UCDs. Different methods can be applied but mutation analysis is the recommended method if the mutation is known in the index-patient. The test requires chorionic villus sampling which should be done around weeks 10-12 of gestation; the result will be available within few days. Close collaboration with the lab offering the test is necessary to ensure timely results.

Genetic counseling should be done well in advance to any pregnancy to carefully consider the different options. Ideally, counseling is offered jointly by geneticists and metabolic specialists.

Management and treatment

a) Basic (well-day) treatment

- General aspects: patients with UCDs should be treated in metabolic centers because they need an interdisciplinary team including metabolic specialists, dieticians, specialised neurologists and psychologists. Usually, patients will be seen as outpatients every three months to monitor growth, treatment compliance, and amino acid profiles.
- Metabolic therapy comprises dietary treatment and pharmacotherapy:

    1. Dietary treatment: most patients need a protein-restricted diet. The extent of protein restriction can be different in each patient and can be as low as the minimum required for optimal growth. UCD patients always require individual dietary plans which will frequently need to be adapted especially during infancy and childhood. Most patients with dietary protein restriction need supplementation of essential amino acids to avoid malnutrition; in particular, branched chain amino acids (valine, isoleucine and leu-

cine) have been shown to be often decreased in UCD patients. To achieve sufficient supplementation, synthetic amino acid supplements containing essential amino acids might be required. Similarly, vitamins can be decreased in patients on a low protein diet and might also be necessary to be supplemented. A written dietary protocol should be worked out by a specialised dietician.

2. Pharmacotherapy: only a few drugs are available for UCD patients.

    a) Nitrogen scavenger drugs are substances which lead to alternative excretion of nitrogen by bypassing the urea cycle. There are two substances, namely sodium benzoate and sodium phenylbutyrate (being metabolised by the liver to its active metabolite sodium phenylacetate) which conjugate with glycine and glutamine, respectively, allowing for urinary excretion of hippurate and phenylacetylglutamine, respectively. The use of these alternative pathways for nitrogen removal is important for the management of acute episodes of hyperammonemia but also part of long-term treatment of UCD patients.

    Sodium benzoate is not available as a licensed drug (however, in combination with sodium phenylacetate available as Ammonul®, Ucyclyd Pharma) but as a chemical only (for oral/enteral and intravenous use) and patients need to be informed on this. Sodium phenylbutyrate is available as a licensed drug (Ammonaps®, Swedish Orphan) for oral/enteral use.

    b) Arginine and citrulline are intermediary metabolites of the urea cycle and are used in UCD patients as drugs. One reason is that arginine becomes an essential amino acid in

most UCDs; to avoid arginine deficiency, supplementation of arginine is performed in most patients. Alternatively, citrulline can be used in defects proximal to the enzyme ASS. A second rationale for giving arginine or citrulline is to use these as vehicle for nitrogen excretion in urine because the residual function of the urea cycle results in urinary excretion of citrulline and/or argininosuccinate.

Arginine and citrulline are not available as licensed drugs for this indication; thus, off label use (oral/enteral and intravenous in case of arginine and oral/enteral in case of citrulline) is required and patients need to be informed on this.

c) Carbamylglutamate (N-carbamyl-L-glutamate) is a structural analogue of N-acetylglutamate, which is product of NAGS and the essential allosteric activator of the first urea cycle enzyme, CPS1. Carbamylglutamate is effective in treating acute hyperammonemia in situations of primary and secondary NAGS deficiency.

Carbamylglutamate is available as a licensed drug (Carbaglu®, Orphan Europe) for oral/enteral use.

- Additional pharmacotherapy: not routinely required but maybe necessary for treatment of complications, e.g. seizures.
- Physiotherapy, occupational therapy: not routinely required but maybe necessary based on individual patient assessment.
- Liver transplantation is currently the only cure for UCD patients. This procedure can be performed with similar rates of morbidity and mortality than in other disorders. For these reasons, liver transplantation should

be considered in UCD patients with a severe metabolic decompensation (but not in NAGS deficiency for which effective pharmacotherapy is available).

- Asymptomatic patients often need no therapy but always need a written emergency prescription. Also, they should be seen by metabolic specialists to ensure adequate counseling for the varying needs during life.

b) Emergency treatment

- Glucose and energy supply during acute hyperammonemic decompensation should be high to reverse protein catabolism as effective as possible and, hereby, to avoid further accumulation of ammonia.
- Protein intake should be stopped during the first 24 hours of any hyperammonemic decompensation but then needs to be re-introduced stepwise to avoid essential amino acid deficiencies.
- Detoxification strategies include bolus doses of drugs and/or extracorporeal measures.

  - Pharmacotherapy as part of emergency treatment comprises use of the above described drugs as intravenous bolus.

  - Hemodialysis/hemofiltration should be prepared in severe hyperammonemic decompensation as ultima ratio and should be started if conventional therapy fails.

Prognosis

The prognosis of most UCD patients largely depends on the duration of coma during the (initial) hyperammonemic decompensation(s). Patients who were in coma for more than 24 hours often die or survive with severe neurological complications. This underlines the need for a high level of suspicion in healthcare

professionals and the recommendation for early ammonia measurements in any patient with an unexplained change in consciousness. Patients in which the initial hyperammonemic decompensation could be managed rapidly and who don't experience recurrent hyperammonemic episodes have a much better prognosis.

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For more information: http://ec.europa.eu/health/programme/policy/index_en.htm

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