Clinical Manifestations of Inborn Errors of the Urea Cycle and Related Metabolic Disorders during Childhood[1]

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ABSTRACT Various disorders cause hyperammonemia during childhood. Among them are those caused by inherited defects in urea synthesis and related metabolic pathways. These disorders can be grouped into two types: disorders of the enzymes that comprise the urea cycle, and disorders of the transporters or metabolites of the amino acids related to the urea cycle. Principal clinical features of these disorders are caused by elevated levels of blood ammonium. Additional disease-specific symptoms are related to the particular metabolic defect. These specific clinical manifestations are often due to an excess or lack of specific amino acids. Treatment of urea cycle disorders and related metabolic diseases consists of nutritional restriction of proteins, administration of specific amino acids, and use of alternative pathways for discarding excess nitrogen. Although combinations of these treatments are extensively employed, the prognosis of severe cases remains unsatisfactory. Liver transplantation is one alternative for which a better prognosis is reported. J. Nutr. 134: 1605S–1609S, 2004.

KEY WORDS: • *urea cycle disorders* • *hyperammonemia* • *carbamyl phosphate synthetase* • *ornithine transcarbamylase*

Basic pathogenesis of defects in the urea cycle and related metabolism

In the urea cycle or in urea cycle–related disorders, clinical symptoms are mainly caused by two different mechanisms (**Table 1**). First, symptoms caused by hyperammonemia occur regardless of the specific metabolic defect. Elevated blood ammonium levels cause the chief pathology, because toxicity of ammonium is dominant in most of these disorders. Second, specific conditions caused by an individual metabolic defect can give rise to unique clinical manifestations. The differences seen in patients with different disorders arise from excesses or deficiencies of amino acids and/or related metabolites. Actual clinical manifestations depend on the severity of the metabolic defect and the condition of the patient and include factors such as age, nutritional status, and associated diseases such as infections. As can be seen from the metabolic map (**Fig. 1**), ornithine, citrulline, argininosuccinate, and arginine make up the urea cycle. Citrulline is synthesized by ornithine and carbamyl phosphate. One of the nitrogen atoms of urea is transferred from carbamyl phosphate and another is from aspartic acid. Urea synthesis begins with the synthesis of carbamyl phosphate catalyzed by carbamyl phosphate synthetase (CPS)[3] I. The other known CPS is the enzyme CPS II, which catalyzes the reaction of carbamyl phosphate synthesis from glutamine. Carbamyl phosphate produced with CPS I then reacts with ornithine to make citrulline. Citrulline in turn reacts with aspartic acid to produce argininosuccinate. Up to this point, the excess nitrogen is bonded to amino acids. Argininosuccinate is cleaved into arginine and fumarate. From arginine, urea and ornithine are produced, which completes the cycle. Abnormalities of the enzymes involved in these reactions or an abnormal *N*-acetylglutamate leads to congenital hyperammonemia. It is noteworthy that CPS I and ornithine transcarbamylase (OTC) exist in the mitochondrial matrix, whereas the other enzymes of the urea cycle reside in the cytosol. So for this cycle to function smoothly, ornithine must be transported across the mitochondrial membrane. Abnormalities of this ornithine-transporting protein also cause hyperammonemia. Failure to absorb arginine and ornithine in the digestive tract is another cause of hyperammonemia.

Toxicity of ammonium

The main manifestation that is observed when blood ammonium levels increase is central nervous system dysfunction including stupor, convulsions, and coma. Blood ammonium concentrations are strictly maintained in normal humans at 15–60 μg/dL. The clinical symptoms caused by elevated levels of blood ammonium directly correspond to its levels.

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[3] Abbreviations used: ASS, arginine succinate synthetase; CPS, carbamyl phosphate synthetase; OTC, ornithine transcarbamylase; UCD, urea cycle disorders.

TABLE 1

Urea cycle and related disorders

	Abnormalities of metabolism		
	Excess metabolites	Reduced metabolites	Specific clinical features
CPSI deficiency	Ammonium, glutamate	Citrulline, arginine	—
OTC deficiency	Ammonium, glutamate	Citrulline, arginine	—
Citrullinemia (classical)	Ammonium, citrulline	Arginine	—
Argininosuccinic aciduria	Ammonium, argininosuccinic acid, citrulline	Arginine	Hepatomegaly, twisted hair
Argininemia	—	—	Spastic paraplegia
Gyrate atrophy of retina (OAT deficiency)	Ammonium (transient), ornithine	—	Retinal degeneration
Adult onset citrullinemia type II (citrin deficiency)	Ammonium, citrulline	Arginine	Liver damage
Hyperammonemia-hyperornithinemia-homocitrullinemia syndrome (mutations in ORT1)	Ammonium, ornithine, homocitrulline	—	—
Lysinuric protein intolerance (mutations in SLC25A13)	Ammonium	Lysine, arginine	Hepatosplenomegaly, osteoporosis

When blood ammonium levels exceed 100 μg/dL, appetite loss, nausea, insomnia, agitation, and personality changes emerge. With levels ~150–200 μg/dL, seizures and severe loss of consciousness occur. Sudden elevations of ammonium from normal levels cause a unique flapping tremor of the hands. When levels exceed 200–400 μg/dL, severe coma and respiratory failure lead to life-threatening conditions. However, tolerance to elevated ammonium levels has occurred in patients who have undergone treatment for some time, and some patients are asymptomatic even with levels of ~200 μg /dL. Damage to the central nervous system caused by elevated blood ammonium concentrations appears reversible when levels do not exceed 200–400 μg/dL; however, the damage accumulates and often results in irreversible impairment.

Principles of treatment

Basic procedures for therapy have been established (1,2) that include protein restriction, arginine administration, use of alternative pathways, and mechanical nitrogen excretion. Dietary protein restriction is almost always required. Administration of citrulline and arginine is effective in most cases except for argininemia. In patients with citrullinemia and argininosuccinic aciduria, arginine is essential for treatment.

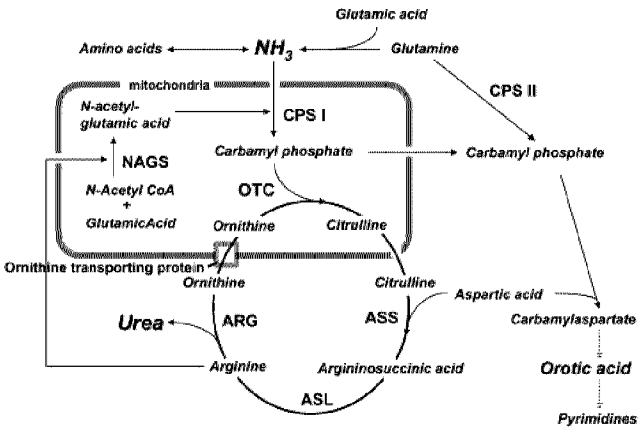

FIGURE 1 The urea cycle. ASL, argininosuccinate lyase; ARG, arginase; NAGS, *N*-acetylglutamate synthetase.

Benzoic acid is conjugated with glycine in the liver and is excreted as a glycine-conjugated form. Accordingly, this process results in excretion of one molecule of glycine. Similarly, phenylacetate is conjugated with glutamine before excretion; two molecules of nitrogen are excreted when one molecule of phenylacetate is administered. Thus, administration of sodium benzoate and sodium phenylacetate results in excretion of excess nitrogen. These drugs, which use alternative pathways to excrete excess nitrogen, are being used in combination with administration of arginine and/or citrulline. Amino acids combined with these two compounds have been used for treatment of urea cycle disorders (UCDs), especially for patients with OTC and CPS deficiencies (**Fig. 2**).

Liver transplantation has been used to treat UCD patients (3,4). In some cases, auxiliary liver transplantation has been successfully performed (5). Considering that the long-term prognosis of patients with UCDs is generally poor, liver transplantation becomes an important treatment (as discussed below).

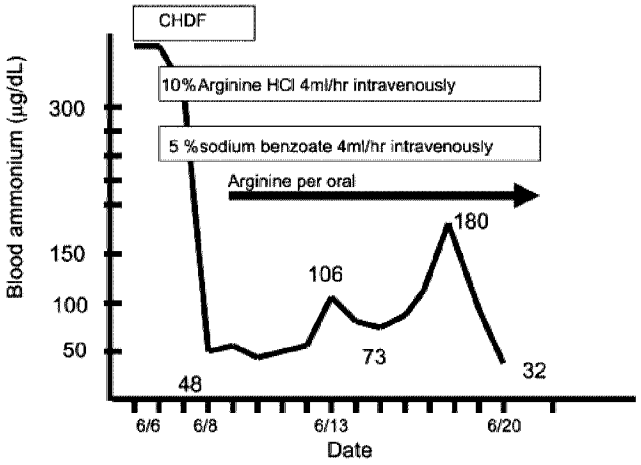

FIGURE 2 A representative clinical course of a hyperammonemia attack in children. Continuous hemodialysis with filtration (CHDF) and intravenous infusion of sodium benzoate and arginine effectively reduced blood ammonium levels in this 4-y-old male patient with OTC deficiency.

Disease-specific pathogenesis

CPS deficiency. CPS deficiency is caused by mutation of the CPS gene and is inherited in an autosomal recessive manner (6,7). The clinical presentation of patients with CPS deficiency is indistinguishable from those with OTC deficiency. With severe enzyme deficiency, patients show neonatal onset of the disease. Adult-onset cases with mild mutations have also been reported. The approach for treatment of CPS deficiency is similar to that for OTC deficiency, and nutritional restriction of protein and administration of arginine/citrulline and sodium benzoate/sodium phenylacetate are employed. Gene analysis of family members has been used for prenatal diagnosis of the disease (8)

OTC deficiency. This is an X-linked inherited disorder of a mutation in the OTC gene (9,10). Male patients usually show clinically severe symptoms at younger ages than female patients. Accordingly, neonatal-onset patients are mostly male with rare exceptions. The most severely affected individuals show increases in ammonium within 1–2 d after birth. The typical clinical features include loss of consciousness, respiratory failure, and seizures, which resemble neonatal sepsis. Patients with less-severe effects manifest their first symptoms later in life, mostly after 1 mo of age, and are referred to as late-onset patients. Symptoms are typically nausea, vomiting, loss of consciousness, and seizures. A specific mutation is reported to cause adult-onset OTC deficiency with high mortality, which suggests that clinical features are influenced by gene mutations (11). Frequent elevation of blood ammonium level is a typical feature in patients who survive the initial attack, although sudden death sometimes occurs among male adult-onset patients. Most female patients show initial symptoms after 1 mo of age; however, levels of ammonium occasionally elevate suddenly to life-threatening levels. Under these conditions, patients should receive intensive treatment including intravenous infusion of effective amino acids and/or drugs to employ alternative pathways to discard excess nitrogen (see below for details). This condition, called acute illness or acute attack, is one of the typical features of patients with UCDs. Acute illness is usually seen in the more severe cases.

Treatment of this disorder depends on the severity of the disease. In mild cases, nutritional restriction of protein intake improves clinical symptoms and prognosis. Many patients should receive oral administration of citrulline and arginine to cope with decreased synthesis of arginine in the urea cycle. Because one amino group is incorporated into citrulline by the reaction of argininosuccinate synthetase, use of this amino acid is essential for severe cases. Alternatively, arginine is an essential amino acid in patients with UCDs except for arginase deficiency. In addition, drugs for alternative pathways such as sodium benzoate and sodium phenylacetate are given for severe cases (12). Liver transplantation is one of the most important treatments in OTC deficiency for both male and female patients. Transplantation from live relative donors including heterozygotes for OTC deficiency has been effective (13).

OTC deficiency is initially suspected based upon high blood ammonium levels and amino acid analysis. Low levels of citrulline and arginine with high levels of glutamate/glutamine are typical features. Elevation of ornithine may be seen but is not essential.

Citrullinemia. Citrullinemia is caused by deficiency of argininosuccinate synthetase and is inherited as an autosomal recessive trait with a mutation in the argininosuccinate synthetase gene (14). Blood levels of citrulline are very high in these patients; however, the clinical symptoms of these patients are apparently due to hyperammonemia. Accordingly, citrulline itself seems harmless. In severe cases, clinical symptoms due to elevated blood ammonium levels develop in the neonatal period, although this progresses slower than in those with severe OTC or CPS deficiency. Amino acid analysis reveals very low levels of arginine in addition to extremely high levels of citrulline, and diagnosis of this disorder can be made based on these findings. Citrin is a mitochondrial aspartate transporter, and its deficiency is one important disease to be distinguished from citrullinemia in the neonatal period (15) (see below).

Treatment of citrullinemia consists of nutritional restriction of protein intake and administration of arginine. Because biosynthesis of arginine is severely affected in these patients, administration of arginine is effective and is an essential part of treatment. The prognosis for patients with this disorder is generally better than for those with OTC or CPS deficiency. However, some degree of mental retardation is seen in most cases.

Argininosuccinic aciduria. This autosomal recessive disorder is due to a loss of argininosuccinate lyase, which produces arginine and fumarate from argininosuccinate (16,17). There is an increase of argininosuccinate in the blood and urine. In addition, severe arginine deficiency is observed, which resembles citrullinemia. Clinical features of this disorder are characterized by hepatomegaly and in some cases abnormally kinky hair as well as hyperammonemia. Elevation of ammonium is mostly due to arginine deficiency, and restriction of arginine and protein is effective. Clinical symptoms are milder compared with those observed with OTC or CPS deficiency; however, severe cases present clinical symptoms during the neonatal period. Mental retardation is observed in almost all patients even when control of blood ammonium has been well achieved. Accumulation of argininosuccinate in body fluids, including the cerebrospinal fluid, might relate to mental retardation in these patients. This leads us to believe that argininosuccinate is not harmless.

Argininemia. Argininemia is caused by deficiency of arginase I, which is present in soluble fractions of hepatocytes (18,19) (arginase II exists in the mitochondria of the liver and kidney). Clinical features of this disorder are characterized by spastic paraplegia as well as intractable mental retardation (20,21). These features are not associated with other types of UCDs and are probably related to the accumulation of arginine in body fluids. Protein restriction is the only measure for prevention or delay of progression of these neurological symptoms. Long-term investigations on patients with arginase deficiency reveal that blood arginine levels are well correlated with the severity of the neurological damage (21). Diagnosis of this disorder is made by amino acid analysis of plasma.

N-acetylglutamate synthetase deficiency. This disorder is caused by mutations in the *N*-acetylglutamate synthetase gene (22,23). *N*-acetylglutamate is required for activation of carbamoyl phosphate synthetase. When synthesis of *N*-acetylglutamate synthetase is limited, a secondary deficiency of CPS is produced. Hence, clinical symptoms of *N*-acetylglutamate synthetase deficiency resemble CPS deficiency. It is one of the most rare disorders of the UCDs. Treatments for this disorder include restriction of protein intake and administration of arginine. Administration of carbamylglutamate, an analog of *N*-acetylglutamate, is also reported to be effective (24).

Defects in amino acid transporters as causes for hyperammonemia. One group of disorders is caused by defects in the transport of amino acids related to functions of the urea cycle (25,26). Lysinuric protein intolerance is caused by mutations in the gene that leads to malabsorption of dibasic amino acids including lysine, arginine, and ornithine (25–27).

Deficiency of arginine results in mild hyperammonemia. This disorder is characterized by hepatosplenomegaly and osteoporosis. Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome is caused by mutations in the ornithine transporter gene, the product of which functions at the inner mitochondrial membrane for ornithine incorporation. As a result of gene mutation, malfunction of the transporter results, which leads to ornithine deficiency in the mitochondria and hence hyperammonemia (28).

Citrin is a mitochondrial aspartate transporter, and mutation in the citrin gene can cause the adult-onset type of citrullinemia (15,29). This disorder is characterized by progressive liver disease that begins during adolescence and results in cirrhosis. During infancy, some individuals who carry homozygous mutations present with liver disease with cholestasis, although these symptoms are transient and self-limited in most cases (30). Activity of hepatic arginine succinate synthetase (ASS) is severely affected, but its activity in other parts of the body is not defective, and there is no mutation in the ASS gene (30). The precise mechanism for the development of liver disease and ASS deficiency has not been elucidated. Because clinical symptoms vary among patients, definitive diagnosis was made possible by gene analysis for several common mutations. This disorder has a higher incidence among East-Asian populations and is one of the most frequent disorders to cause hyperammonemia in adults.

Administration of arginine is effective in ameliorating hyperammonemia; however, the effect is transient. Specific treatment has not been established, and liver transplantation is necessary for cases with liver failure (31).

Long-term management and prognosis

After recovery from the initial attack, which is often associated with a comatose state, the long-term prognosis for patients with UCDs depends on the blood ammonium levels during the chronic phase and the frequency and severity of acute attacks (32). During an acute attack, sudden elevations of ammonium levels and associated symptoms emerge in patients whose blood ammonium levels were controlled at normal or near-normal levels. These conditions are often caused by seasonal infections, high fever, hunger, and surgery. Treatment should aim to decrease blood ammonium levels and includes intravenous administrations of arginine and/or citrulline. In addition, infusion of sodium benzoate and/or sodium phenylacetate should be used for severe cases. To eliminate ammonium from body fluids in severe cases, dialysis or other measures are effective. When ammonium levels decrease and feeding becomes possible, administration of essential amino acids should be gradually increased. Once blood ammonium levels are stabilized, oral administration of natural proteins combined with oral administration of essential amino acids can begin. The degree of damage depends on the level of ammonium and the length of duration (32,33). Despite employment of these treatments, mental injuries of these patients cannot be avoided (33,34). The relative long-term prognoses of patients with UCDs (**Fig. 3**) reveal that the IQs of patients decrease in inverse proportion to the degree of hyperammonemia and frequency of acute attacks (32).

Malnutrition and deficiencies of essential amino acids as well as other essential nutrients are problems associated with treatment for UCDs. Symptoms caused by essential amino acid deficiency such as eruptions, intractable diaper rash, redness, and skin exfoliation of the extremities should be treated. DNA diagnosis is employed in most of the disorders and has been effectively used for assessments of severity, inheritance patterns, carrier detection, and prenatal diagnosis of UCDs.

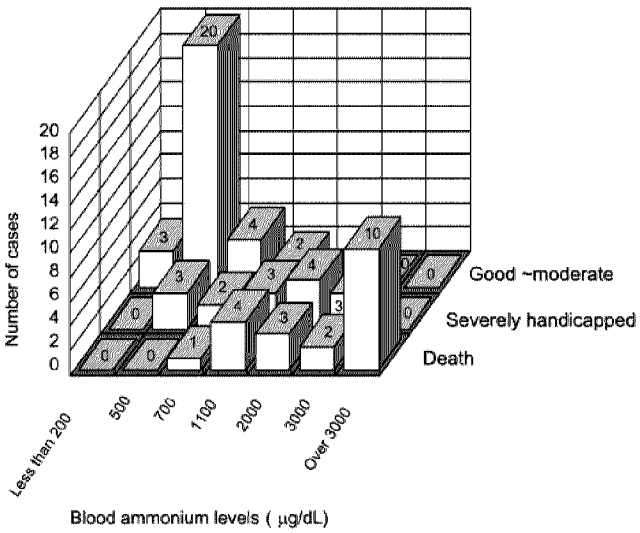

FIGURE 3 Blood ammonium levels at onset and long-term prognoses.

Conclusion

Although advances in the diagnosis and treatment of UCDs are responsible for saving many lives, the mental development of many patients is still affected. Liver transplantation is a promising cure for enzyme deficiency; however, brain damage caused by the initial hyperammonemia attack is inevitable in many patients even with newborn screening systems. New strategies for diagnosis and prevention of the initial attack must be considered.

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