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Clinical, Biochemical, and Molecular Spectrum of Hyperargininemia Due to Arginase I Deficiency

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Abstract

The urea cycle consists of six consecutive enzymatic reactions that convert waste nitrogen into urea. Urea cycle disorders are a group of inborn errors of hepatic metabolism that often result in life threatening hyperammonemia and hyperglutaminemia. Deficiencies of all of the enzymes of the cycle have been described and although each specific disorder results in the accumulation of different precursors, hyperammonemia and hyperglutaminemia are common biochemical hallmarks of these disorders. Arginase is the enzyme involved in the last step of the urea cycle. It catalyzes the conversion of arginine to urea and ornithine. The latter reenters the mitochondrion to continue the cycle. Hyperargininemia is an autosomal recessive disorder caused by a defect in the arginase I enzyme. Unlike other urea cycle disorders, this condition is not generally associated with a hyperammonemic encephalopathy in the neonatal period. It typically presents later in childhood between 2 and 4 years of age with predominantly neurological features. If untreated, it progresses with gradual developmental regression. A favorable outcome can be achieved if dietary treatment and alternative pathway therapy are instituted early in the disease course. With this approach, further neurological deterioration is prevented and partial recovery of skills ensues. Early diagnosis of this disorder through newborn screening programs may lead to a better outcome. This review article summarizes the clinical characterization of this disorder; as well as its biochemical, enzymatic, and molecular features. Treatment, prenatal diagnosis and diagnosis through newborn screening are also discussed.

Keywords

arginase I; arginine; hyperargininemia; urea cycle

INTRODUCTION

The urea cycle disorders are a group of inborn errors of hepatic metabolism that affect the transfer of waste nitrogen into urea. The urea cycle (Fig. 1) has two main functions: the detoxification of waste nitrogen into excretable urea and the *de novo* biosynthesis of arginine [Brusilow and Horwich, 2001]. Deficiencies of all of the enzymes of the urea cycle have been identified, and although each specific disorder results in accumulation of different metabolites, they (except for hyperargininemia) usually present in the newborn period or in early infancy with hyperammonemic encephalopathy and hyperglutaminemia [Batshaw et al., 1980; Maestri et al., 1999; Msall et al., 1984]. Most of these disorders (N-acetyl glutamate synthase deficiency, carbamoyl phosphate synthetase I deficiency, argininosuccinate synthetase deficiency, argininosuccinate lyase deficiency, and arginase I deficiency or hyperargininemia) are inherited in an autosomal recessive fashion, whereas ornithine transcarbamylase deficiency is X-linked [Maestri et al., 1998]. The overall prevalence of these conditions is estimated to be of 1:8200 in the United States [Brusilow and Maestri, 1996]. Ornithine transcarbamylase deficiency has the highest prevalence of the six urea cycle defects while hyperargininemia and N-acetyl glutamate synthase deficiency are the least frequent.

Hyperargininemia (OMIM 207800) is caused by a defect in the hydrolysis of arginine to urea and ornithine by the enzyme arginase I [ARG1 (EC 3.5.3.1)]. It has an estimated incidence of 1 in 2,000,000 live births [Nagata et al., 1991; Naylor, 1981] and it affects 3/7,000 institutionalized individuals with mental retardation [Naylor et al., 1977].

The first documented cases of this condition were published in 1969 describing two sisters born to consanguineous parents who exhibited periodic vomiting, anorexia, lethargy, cognitive impairment, and a seizure disorder [Terheggen, 1969]. Urine amino acid analysis revealed increased excretion of cystine, lysine, ornithine, and arginine. In blood, hyperargininemia and hyperammonemia were found. The disease is pan-ethnic. An increased incidence of the disease may occur in the French Canadian population due to a founder effect in the lake region of Northern Quebec [Lemieux et al., 1988; Qureshi et al., 1983].

CLINICAL CHARACTERISTICS

Patients with hyperargininemia manifest a neurological syndrome unlike that observed in other urea cycle disorders that consists of cognitive deficits, epilepsy, and progressive spastic diplegia [Iyer et al., 1998]. The pathogenesis is not well understood. In general, this condition does not present in the newborn period and a catastrophic neonatal presentation with hyperammonemia is uncommon. The majority of our patients had a normal neonatal period. A comprehensive review of 55 patients with hyperargininemia indicated that all but three patients (including a few cases with neonatal presentation) were asymptomatic in early infancy [De Deyn, 1997]. Infants usually become irritable, and develop feeding difficulties and decreased alertness when cow's milk is introduced [De Deyn, 1997]. Clumsiness and failure to thrive with short stature may be noted in early childhood with psychomotor deterioration noted from three months to four years of age. If untreated, the course of the

disease becomes slowly progressive in comparison with other urea cycle disorders and leads to loss of developmental milestones and spasticity. Some patients may display intermittent episodes of irritability, feeding difficulties, vomiting, and lethargy that require symptomatic treatment in addition to intravenous use of ammonia scavenger medications [Crombez and Cederbaum, 2005].

Recently, a more unusual rare neonatal presentation of arginase deficiency has been described [Picker et al., 2003]. The propositus had markedly elevated plasma arginine and CSF glutamine, and modestly elevated blood ammonia with tachypnea followed by seizures and cerebral edema. It was thought that the cerebral edema and the fatal course were due to the increased intracellular osmolarity of the elevated glutamine.

On physical exam, the most prominent physical findings are consistent with upper motor neuron involvement in 80% of the patients [De Deyn, 1997] with spastic paraparesis. In almost half of the patients these signs seem to be confined to the lower extremities. The remainder of the neurological examination may be relevant for hyperreflexia, toe walking, loss of cognitive abilities, and failure to thrive. If seizures are present, they are not linked to or caused by hyperammonemia. The predominant seizure type is generalized tonic clonic. Ataxia and athetoid movements are less common neurological features. Brain imaging demonstrates mostly cerebral but also cerebellar atrophy and high signal intensities on T₂ weighted images in periventricular white matter. Patients do not exhibit hearing or visual impairments. Microcephaly has been described in some patients. Electroencephalographic measurements have been abnormal in most patients showing diffuse slowing of background activity and epileptogenic activity in more than 50% of the patients evaluated thus far. Nerve conduction studies of peripheral nerves have been normal. When the spasticity is severe it can lead to secondary skeletal abnormalities. If patients with this condition are exposed to valproic acid, they can develop a hyperammonic encephalopathy as documented in one case [Christmann et al., 1990].

Hepatomegaly has been observed in a minority of patients and could be associated with acute hyperammonemic episodes. Liver dysfunction including cirrhosis has been reported. One patient with hyperargininemia presented with persistent neonatal jaundice, hepatomegaly and evidence of hepatic cirrhosis on liver biopsy [Braga et al., 1997]. We have observed elevated liver enzymes and mild clotting abnormalities in at least three siblings with this condition although none of these patients have demonstrated severe liver disease. Other groups have also found persistent abnormalities of clotting studies in two other patients [Crombez and Cederbaum, 2005].

BIOCHEMICAL ABNORMALITIES

Accumulation of arginine, which is the substrate proximal to the metabolic block, is the biochemical hallmark of hyperargininemia and it is present in all patients. When the first patients were detected, the first finding was a urine amino acid pattern reminiscent of cystinuria with argininuria and increased excretion of other dibasic amino acids together with cystine. This pattern is due to competitive inhibition of tubular reabsorption of these amino acids by excess arginine [van Sande, 1971].

In blood, arginine levels can be increased more than 15-fold [Grody et al., 1993] and in many patients their levels can remain fairly steady, with minimal response to variations in protein intake [Cederbaum et al., 1979]. Arginine levels can be increased up to 10 fold in the cerebrospinal fluid and these levels decrease after therapy has been instituted [Cederbaum et al., 1979].

Blood urea nitrogen is often low in hyperargininemia, but usually not as decreased as in other urea cycle defects [Cederbaum et al., 1979].

The typical crisis associated with hyperammonemia usually observed in other urea cycle defects is rarely seen in hyperargininemia. Peak ammonia levels are usually not as high as in other urea cycle defects. However, at least two patients have died during episodes of hyperammonemic encephalopathy triggered by infections with fairly high ammonia levels [Crombez and Cederbaum, 2005; Grody et al., 1993]. If hyperammonemia is present, hyperglutaminemia may be present as well.

Orotic aciduria can be observed in this condition even in the absence of hyperammonemia. In hyperargininemia, the metabolic block is far removed to cause an accumulation of carbamoyl phosphate due to simple feedback inhibition. Bachmann and Colombo [1980] suggested that a potential cause for pyrimidine synthesis (and orotic aciduria) in this disorder is the stimulating effect of arginine on N-acetylglutamate synthesis with resulting activation of carbamoyl phosphate synthase I.

There is an increase in guanidino compounds derived directly from arginine in many patients with hyperargininemia [Marescau et al., 1990; 1992a; Marescau, 1992b], but their effect on the pathogenesis of disease remains unclear.

As previously stated, liver dysfunction with increased transaminases and clotting abnormalities may occur in association with hyperargininemia as in other urea cycle defects.

Enzyme activity in patients with hyperargininemia is characterized by a deficiency of type I arginase. The enzyme activity can be measured in liver or more conveniently in red blood cells [De Deyn, 1997]. There is good correlation between liver and red blood cell enzyme activity [Cederbaum et al., 1979; Grody et al., 1993]. White blood cell arginase enzyme activity may also be diagnostic [Cederbaum et al., 1979]. It had been speculated that the milder course and less frequently observed hyperammonemia in hyperargininemia when compared with other urea cycle defects could be the result of a second isoenzyme.

This suspicion was confirmed with the identification of mitochondrial arginase activity that becomes up-regulated when the cytosolic arginase I activity in the liver is deficient [Grody et al., 1989; Picker et al., 2003; Spector et al., 1983]. In some cases, mitochondrial arginase can increase up to 40-fold [Crombez and Cederbaum, 2005]. The induction of higher levels of arginase II under conditions of hyperargininemia and hyperammonemia may be responsible for residual ureagenesis in this condition.

PATHOLOGY

Liver biopsy performed during acute decompensation episodes in patients with arginase deficiency has revealed swelling of hepatocytes with minimal signs of fibrosis. These findings might be explained by a known tendency of hyperammonemia of causing changes in hepatocytes. Electron microscopic and histochemical studies have shown hydropic changes, and increased intracellular glycogen. In few patients, portal fibrosis, cirrhosis and enlarged mitochondria in the hepatocytes have been reported [De Deyn, 1997].

Neuropathology reveals cerebral atrophy in concordance with the atrophy found in brain imaging studies. In one subject, myelin pallor was seen in crossed pyramidal tracts, possibly correlating with the pyramidal signs observed in the lower extremities of this individual [De Deyn, 1997].

PATHOGENESIS OF DISEASE

It is unlikely that elevated plasma ammonia is the main neurotoxic compound in hyperargininemia because hyperammonemia rarely occurs in this condition. The extreme spasticity observed in this disorder is not found in other urea cycle defects and the frequent epileptic symptomatology is seldom related to hyperammonemic episodes [Terheggen et al., 1982]. Patients diagnosed and treated since birth with protein restriction and essential amino acid supplementation remain asymptomatic with the oldest patients being more than 35 years of age [Cederbaum et al., 2004] suggesting that chronically elevated levels of arginine may play a direct role in the neuropathology.

Thus, one could argue that in most cases these neurological complications could result from the accumulation of arginine and its metabolites. Patients with hyperargininemia who exhibited normal ammonia levels due to protein restriction but persistently elevated arginine levels, did not experience an amelioration of their clinical condition [Cederbaum et al., 1977; Terheggen et al., 1975]. Several guanidino compounds increased in patients with hyperargininemia are known to be *in vitro* and *in vivo* neurotoxins. Guanidino compounds accumulate in other medical conditions such as uremia and epilepsy leading to speculate that these compounds might contribute to the neurological dysfunction observed in these disorders [De Deyn et al., 1986; Hirayasu et al., 1990]. Some guanidino compounds that are elevated in uremia inhibit the activity of transketolase and it is plausible that in doing so they may produce demyelination with consequent upper motor neuron signs [Lonergan et al., 1971]. α -keto- δ -guanidinovaleric acid and other guanidino compounds found in hyperargininemia counteract the response to inhibitory amino acids in mouse neurons in cell culture, a feature shared by several epileptogenic agents [De Deyn et al., 1988]. The most potent inhibitory agent of GABA and glycine responses in cultured mouse neurons was argininic acid, followed by α -keto- δ -guanidinovaleric acid, homoarginine and arginine [De Deyn et al., 1991]. α -keto- δ -guanidinovaleric acid has been reported to cause seizures in rabbits. Thus, it is possible that the guanidino compounds that accumulate in patients with this condition may affect GABAergic neurotransmission resulting in epileptogenic properties. These compounds may induce seizures by decreasing the fluidity of the plasma membrane [Hiramatsu, 1992]. The Na^+ , K^+ -ATPase is necessary to maintain ionic gradients

for neuronal excitability and is highly responsive to changes in membrane fluidity [Wheeler et al., 1975]. There is evidence that this enzyme activity is decreased in experimental and human epilepsy [Grisar, 1984]. Moreover, the guanidino compounds that accumulate in hyperargininemia, *N*-acetylarginine, homoarginine, and argininic acid significantly inhibited Na^+ , K^+ -ATPase activity in the cerebral cortex of rats at concentrations similar to those observed in CSF and plasma of patients with hyperargininemia [da Silva et al., 1999].

It is thought that arginine modulates neuronal survival through its ability to function as substrate for nitric oxide synthase (NOS) [Esch et al., 1998]. Arginine, *N*-acetylarginine, homoarginine, and argininic acid induced free radical defenses and decreased antioxidant defenses *in vitro* [Wyse et al., 2001]. These compounds inhibited the activities of catalase, superoxide dismutase, and glutathione peroxidase, the main enzymatic defenses in the brain against oxidative damage, at concentrations reminiscent of those observed in patients with hyperargininemia [De Deyn et al., 1991]. All of these mechanisms may contribute to the pathogenesis of the neurological dysfunction in hyperargininemia.

The transfer of nitrogen through the urea cycle into nitric oxide (NO) was studied in two siblings with hyperargininemia using a stable isotope protocol to measure nitrogen flux [Scaglia et al., 2004]. Both siblings exhibited comparable urea appearance rates but they were lower than control values. One of the siblings exhibited more adequate metabolic control when maintained on a protein restricted diet (0.4 g/kg/day) with a normal steady-state arginine level, while the other sibling had a significantly higher steady-state arginine level. The enrichment of ^{15}N into total NO metabolites (NO_x) was significantly higher in the sibling with higher serum arginine levels *versus* the sibling with normal serum arginine, suggesting a correlation between plasma arginine levels and the fractional transfer of ^{15}N -amide glutamine into ^{15}N arginine-imidino nitrogen into $^{15}\text{NO}_x$. Even though these subjects were studied at steady state on protein restriction, plasma NO_x levels are likely confounded by dietary contribution. Hence, further studies to measure the actual flux of NO metabolites from either exogenous or endogenous sources of arginine will be required to elucidate the full effect of arginine production by the cell on NO production. This is important since previous literature has suggested differential utilization of exogenous *versus* endogenously produced arginine by arginase I in the cell [Palacios et al., 1970]. Clearly, while total body flux measurements have lent tremendous insight into the pathomechanisms of these conditions, consideration of intracellular and subcellular compartments will be important.

MOLECULAR CHARACTERISTICS

The gene encoding arginase I, *ARG1*, was cloned in 1986 [Dizikes et al., 1986; Haraguchi et al., 1987] and a number of mutations have been found in this gene. A second gene (*ARG2*) encodes arginase II that has similar biochemical characteristics to arginase I, but is located in the mitochondrial matrix and is expressed in kidney and prostate [Vockley et al., 1996]. The function of arginase II is not very well known [Grody et al., 1993].

Hyperargininemia is caused by heterogeneous mutations in the *ARG1* gene. Nonsense mutations have been reported in a minority of patients, with missense mutations being more prevalent [Uchino et al., 1995; Vockley et al., 1996; Vockley et al., 1994]. Many of these

missense mutations occur in highly conserved regions of the gene [Vockley et al., 1996]. Missense mutations modify the structure and function of the enzyme by distorting the active sites required for the enzymatic reaction, by altering the protein scaffolding and ultimately by interfering with the assembly of the protein trimer [Ash et al., 1998].

ANIMAL MODELS

A mouse knockout model for the *ARG2* gene has been generated [Shi et al., 2001]. Surprisingly, the phenotype of the animals was normal. Plasma arginine in the homozygous mutant animals was significantly higher than in the wild type animals. A knockout mouse for the *ARG1* gene has also been generated [Iyer et al., 2002]. The level of *ARG1* mRNA was virtually zero with undetectable protein levels. The animals are smaller and die of hyperammonemia at 12 days of age. Arginine levels are increased more than four-fold. *ARG1* and *ARG2* knockout mice have been generated [Cederbaum et al., 2004], however, results from studies to evaluate the phenotype of the homozygote *ARG2* knockout, heterozygous *ARG1* knockout have not been published yet.

PRENATAL DIAGNOSIS

If the mutations in the *ARG1* gene are known, prenatal diagnosis can be performed by mutation analysis in chorionic villous tissue or amniocytes. Arginase I is expressed in fetal red cells at 16-20 weeks of gestation at comparable levels to the postnatal levels [Spector et al., 1980]. Percutaneous umbilical blood sampling has been used to predict a normal outcome [Hewson et al., 2003] and an affected pregnancy [Snyderman et al., 1979].

NEWBORN SCREENING PROGRAM

The success of neonatal screening for phenylketonuria and the availability of new techniques such as tandem mass spectrometry has led to efforts to include the urea cycle defects in newborn screening programs. The progress made in the treatment of urea cycle defects presenting in the neonatal period has clearly improved the survival of patients during the first 2-3 years of life, but at the cost of having patients with psychomotor retardation. Early treatment after detection by newborn screening could improve this outcome.

Arginine can be measured by mass spectrometry and the diagnosis of a patient with hyperargininemia from newborn screening has already been reported [Picker et al., 2003]. A survey among participants of a listserve for metabolic specialists revealed four more cases diagnosed by newborn screening and one case that was missed [Crombez and Cederbaum, 2005]. Although these findings are encouraging, it is possible that some cases may be missed when the screening is done too early in the newborn period. Further research is necessary to determine the sensitivity of tandem mass spectrometry to detect hyperargininemia. An alternative method based on direct enzyme assay has yet to yield a positive result in 500,000 newborns screened [Chace et al., 2002].

MANAGEMENT AND TREATMENT OF ARGININEMIA

Treatment of hyperargininemia focuses on dietary protein restriction, supplementation of essential amino acids, and the use of alternative pathways to remove the nitrogen waste [Iyer et al., 1998]. Treated patients tend to have fewer and more easily controlled hyperammonemic crises, and therefore, early diagnosis is needed because early nutritional management could be successful in controlling the deleterious neurological effects observed in this condition. In these patients, there is ample evidence that effective therapy stops the progressive neurological deterioration.

Diet plays a key role in the treatment of hyperargininemia since it is considered a metabolic disease that responds to dietary therapy [Snyderman et al., 1977]. Dietary treatment alone in this condition improved arginine levels to near normal in plasma and CSF [Cederbaum et al., 1982; De Deyn, 1997; Snyderman et al., 1979]. The patients experienced improvement in their neurological status with amelioration of spasticity, increased linear growth, and restoration of limited speech among other functions. Besides the limitation of natural protein intake, patients should be supplemented with essential amino acids, and protein intake could be provided as a combination of complete protein (50% to 75%) and essential amino acids (25% to 50%). In our experience, it is difficult for the majority of patients to adhere to a rigorous diet that would bring arginine levels near a normal range.

The alternative pathway therapy includes the use of sodium benzoate and sodium phenylbutyrate (Fig.2) to stimulate the excretion of nitrogen in the form of hippuric acid and phenylacetylglutamine, respectively [Batshaw et al., 2001]. The emergence of this therapy allowed to monitor its effect in patients with hyperargininemia [Iyer et al., 1998; Qureshi et al., 1984]. Using this therapeutic modality, patients appear to maintain stable neurological function, with some increase in spasticity as they become older. Three patients treated from birth (including two patients in their thirties) have remained largely asymptomatic [De Deyn, 1997].

The use of sodium phenylbutyrate has been linked to branched chain amino acid depletion in urea cycle defect patients [Scaglia et al., 2004], and therefore we currently recommend frequent monitoring of branched chain amino acids levels and supplementation with these amino acids if a deficiency arises.

While the lower extremities spasticity may progress despite treatment, it can be treated in an effective manner by botox injections or tendon-release procedures via heel cord lengthening [Cederbaum et al., 2004].

CONCLUSION

Hyperargininemia due to deficiency of arginase I is a treatable inborn error of the urea cycle. This condition rarely presents in the newborn period and hyperammonemia is not a common biochemical hallmark. The accumulation of arginine and related guanidino compounds may contribute to the pathogenesis of disease. The advent of new techniques allows to screen for this condition in the newborn period. If good compliance with the dietary and alternative pathway therapy is instituted, a favorable outcome can be expected, with potential

improvement of neurological features. The existence of a second locus for arginase may provide a unique approach to treatment in the future if the expression of this gene could be enhanced.

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Biographies

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Figure 1. The Urea Cycle

The urea cycle (UC) converts nitrogen, derived from dietary protein intake and the catabolic breakdown of endogenous protein into urea, which is readily excreted from the body.

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Figure 2.
Alternative Pathway Therapy for Urea Cycle Disorders (UCD)