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Minireview

Hyperargininemia due to liver arginase deficiency

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Abstract

The urea cycle is a series of six reactions necessary to rid the body of the nitrogen generated by the metabolism, primarily of amino acids, from the diet or released as the result of endogenous protein catabolism. Arginase is the sixth and final enzyme of this cycle. Arginase catalyzes the conversion of arginine to urea and ornithine, the latter recycled to continue the cycle. Hyperargininemia due to arginase deficiency is inherited in an autosomal recessive manner and gene for arginase, designated AI, has been cloned. Unlike the other urea cycle enzymes, a second gene encoding arginase, with similar structural properties and enzyme characteristics, exists and has been named Arginase II (AII). Comprehensive histories and physical examinations confirm a strikingly uniform clinical picture and one notably different from patients with other urea cycle disorders. This condition rarely presents in the neonatal period and first symptoms typically present in children between 2 and 4 years of age. First symptoms are often neurologically based. If untreated, symptoms are progressive with a gradual loss of developmental milestones. With adherence to a dietary and drug regimen, a favorable outcome can be expected, with cessation of further neurological deterioration and in some instances, of improvement. This article summarizes the clinical course of selected patients who represent the full spectrum of presentations of arginase deficiency. In addition to the clinical characterization of this disorder; the biochemical, enzymatic, and molecular evidence of disease is summarized. Treatment and prenatal diagnosis are also discussed.

Keywords: Arginine; Arginase; Urea cycle; Treatment

Introduction

The urea cycle is a series of six reactions that have been recruited to rid the body of waste nitrogen (Fig. 1). Arginase is the sixth and final enzyme of this cycle and the most recently evolved; the others having been present for arginine biosynthesis in lower organisms [1]. Arginase catalyzes the conversion of arginine to urea and ornithine, the latter recycled to continue the cycle. The first three enzymes, *N*-acetyl-glutamate synthase (NAGS), carbamoyl phosphate synthase I (CPSI), and ornithine transcarbamylase (OTC) function inside of the mitochondria whereas the latter three, argininosuccinic acid synthase, argininosuccinic acid lyase, and arginase, act in the cytosol [1]. At least two transporters, for ornithine and citrulline (ORNTI) [2] and aspartate (citrin) [3] are also critical to the process. The waste nitrogen for this cycle is generated by the metabolism, primarily of amino acids, either ingested in the diet or released as the result of endogenous protein catabolism [1]. The liver is the only organ in the body to contain all of the enzymes needed for the function of the urea cycle.

Defects of all six steps of the urea cycle are known [1]. All may result in defective function of the cycle and in

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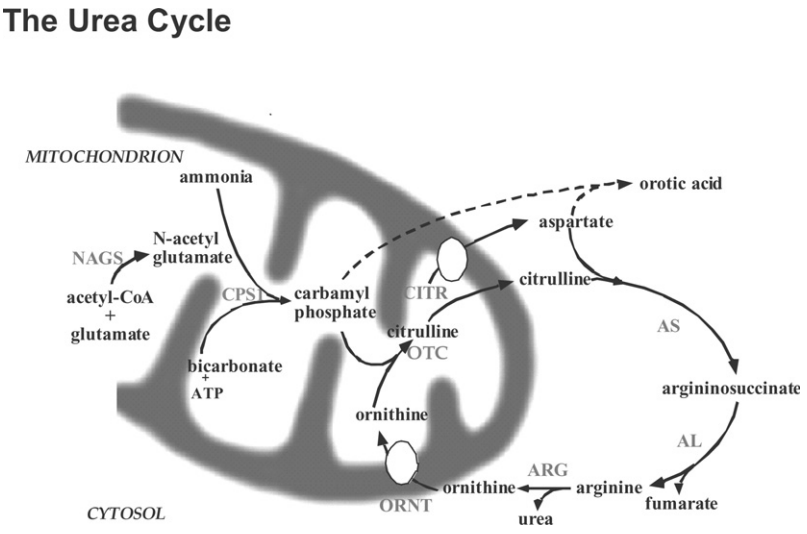

Fig. 1. The urea cycle. The six primary enzymatic steps of the urea cycle are shown in bold capital letters. NAGS, *N*-acetylglutamate synthase; CPSI, carbamylphosphate synthase; OTC, ornithine transcarbamylase; AS, argininosuccinic acid synthase; AL, argininosuccinic acid lyase; and ARG, arginase. ORNT and CITR are respectively, the ornithine and aspartate transporters. Their function is necessary for the movement of substrates in and out of the mitochondrion. Reprinted with permission from Tuchman and Bradshaw [47].

the accumulation of excess ammonia in the body, either continuously or intermittently, with resulting neurological damage, developmental delay, and mental retardation. Defects in any of the first five steps of the cycle have been reported to cause acute neonatal or acute intermittent hyperammonemia.

Hyperammonemia has infrequently been associated with arginase deficiency and presentation in the neonatal period is an uncommon event [4]. Ornithine transcarbamylase deficiency has the highest incidence of the six disorders and arginase and NAGS deficiencies have the lowest incidence. This is ascertained from the number and timing of the case reports, from a fairly comprehensive survey of urea cycle disorders in Japan [5] and from the screening of at least 7000 developmentally handicapped individuals in an institution for the mentally retarded in which no cases of arginase deficiency were ascertained [6]. The true incidence of arginase and NAGS deficiencies is unknown.

The first case of arginase deficiency was probably reported in 1965 by Peralta Serrano [7], but no comprehensive evaluation or enzymatic assay was done. The first family known to have this disorder was reported by Terheggen and associates in 1969 [10–13]. Subsequently, more than 30 cases have been reported in the literature and a larger number are known to our metabolic team and to DeDeyn et al. [8] who published a review in the proceedings of a conference on guanidino compounds, held in Montreal in 1994. The summary material in this article derives from our own extensive experience and the collective experience reflected in that article, encompassing professor DeDeyn's remarkable feat of having visited the majority of known patients in the world prior to that time. The disorder is inherited in an autosomal recessive manner with frequent instances of consanguinity. A pocket of increased frequency may occur amongst the French Canadian due to a well known bottleneck in the founder population of the lake region of northern Quebec province [9].

The gene for liver arginase, designated AI, was cloned in 1986 by Mori and co-workers [10] and ourselves [11,12] and we have subsequently defined a number of natural mutations in the gene [12–14]. Ash and co-workers [15] have crystallized rat liver arginase and have super-imposed the homologous human enzyme on the coordinates derived from the rat. In addition, the perturbation in protein structure and function caused by these mutations has been described [16]. Unlike the other urea cycle enzymes, a second gene encoding arginase, with similar structural properties and enzyme characteristics, exists and has been named Arginase II (AII) [17–20]. Arginase II is most abundantly expressed in kidney and prostate and is located in the mitochondrial matrix. It appears to be induced in AI deficiency and may mitigate the degree of hyperargininemia and hyperammonemia in this disease [21]. The function of AII is not well-defined or proven and is subject of intense study.

Clinical presentations and course

The patients whom we have seen represent the full spectrum of presentations. Thus we have chosen to report them as individuals.

Patient 1, now 13 years, was diagnosed at 4 years of age after presenting with growth failure starting at 2 years, gait abnormalities since 3 years, bilateral lower extremity spasticity, and a seizure disorder. Physical examination on presentation showed growth failure, decreased range of motion, increased tone, and extreme