Clinical Biochemistry 45 (2012) 1583–1586

Contents lists available at SciVerse ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Recurrent unexplained hyperammonemia in an adolescent with arginase deficiency

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ARTICLE INFO

Article history:
Received 29 May 2012
Received in revised form 10 August 2012
Accepted 12 August 2012
Available online 23 August 2012

Keywords:
Hyperammonemia
Pre-analytical variations
Arginase deficiency
Urea cycle disorders

ABSTRACT

Objectives: This report investigates the etiology of recurrent episodic elevations in plasma ammonia in an adolescent male with arginase deficiency as there were concerns regarding pre-analytical and analytical perturbations of ammonia measurements. There were repeated discrepancies between the magnitude of his ammonia levels and the severity of his clinical signs of hyperammonemia.

Patient and methods: The patient is a fourteen-year-old arginase-deficient male diagnosed at three years of age. Since 2008 (when he reached 10 years of age), there appeared to be an increase in the frequency of hospitalizations with elevated ammonia. A typical emergency visit with initial ammonia of 105 μmol/L (reference interval: 16–47 μmol/L) is illustrated. Pre-analytical and analytical procedures for the patient's sample handling were retrospectively examined.
His ammonia levels were compiled since diagnosis. The frequency of his initial or peak ammonia levels greater than two times (94 μmol/L) or four times (188 μmol/L) the upper limit of normal was computed. Student t-test was used to calculate the significance of the differences before 2008 and since 2008.

Results: One out of eleven and ten out of 19 hospitalizations had initial ammonia greater than two times normal before and after 2008, respectively. Both the patient's overall ammonia and peak ammonia levels are significantly higher since 2008 (p value < 0.001 for both) than those before 2008.

Conclusions: To our knowledge, few adolescent males with arginase deficiency experience recurrent episodes of hyperammonemia requiring intravenous nitrogen scavenging agents. We hope that this study provides new insights into the natural history of arginase deficiency and the management of such patients.

Introduction

The urea cycle consists of six consecutive enzymatic reactions to remove excess ammonia that is generated during the catabolism of nitrogen-containing compounds from the body [1]. Ammonia is in equilibrium with glutamine and is converted to urea through the urea cycle. Plasma ammonia concentrations are maintained within a fairly narrow range (reference interval [RI]: 16–47 μmol/L). Elevations are usually associated with acquired liver disease such as liver cirrhosis or severe hepatitis, or with certain organic acid disorders (propionic acidemia) or urea cycle disorders. Hyperammonemia, with one or several clinical signs of lethargy, confusion, irritability, vomiting, seizure, tremor, and coma, is a medical emergency requiring immediate medical attention [1]. Prolonged exposure to high ammonia can lead to severe central nervous system damage and even death [1].

Arginase deficiency (also known as hyperargininemia, Mendelian Inheritance in Man number 207800), is caused by a deficiency of liver enzyme arginase I (E.C. 3.5.3.1). It is the least common urea cycle disorder with an estimated prevalence of 1 in 1,100,000 [2]. Arginase, the last enzyme in the urea cycle, catalyzes the conversion of arginine to urea and ornithine (Fig. 1). Urea is excreted in the urine, and ornithine is transported to the mitochondria to continue the cycle.

Clinical manifestations of arginase deficiency are strikingly different from the other urea cycle disorders. As opposed to other urea cycle disorders that may present 24 to 72 h after birth or occasionally several days later into the extended neonatal period, arginase deficiency rarely presents in the neonatal period and first symptoms typically present in children between two and four years of age [3]. Hyperammonemia is not typically associated with arginase deficiency [4]. When hyperammonemic encephalopathy occurs, the plasma ammonia levels are three to four times normal value, with levels rarely greater than six times normal. These patients can become comatose

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0009-9120/$ – see front matter
http://dx.doi.org/10.1016/j.clinbiochem.2012.08.015

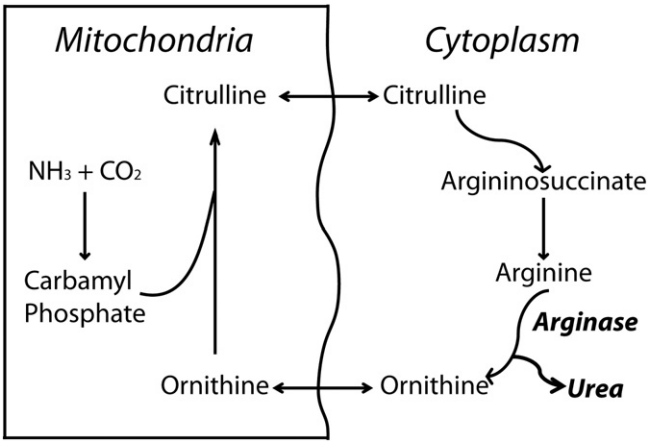

Fig. 1. Schematic of the urea cycle. Arginase is the last enzyme in this cycle which converts arginine to ornithine and urea.

when their ammonia levels rise to three to four times normal and may succumb to lethal brain edema [5].

Although not well studied, elevated arginase II, the mitochondria form of arginase expressed in kidney and brain, has been reported to be further induced by increased arginine levels in patients with arginase deficiency [6,7]. Arginase II may be the major contributor to the generally milder clinical presentations in these patients in comparison to other urea cycle disorders [5]. The less severe clinical course for arginase deficiency may also be due to the fact that arginase is at the last step of the urea cycle and two molecules of ammonium ions have already been accumulated into L-arginine by this point.

In this report, we describe a male with arginase deficiency who had multiple episodes of hyperammonemia that required intravenous nitrogen scavenging medications between 10 and 14 years of age. In the majority of these episodes, he demonstrated less severe clinical presentation than expected based on the high ammonia levels. One typical emergency hospital visit is illustrated here during which he did not show typical clinical signs of hyperammonemia even at ammonia levels of 252 μmol/L and 242 μmol/L. This significant discrepancy triggered an investigation in the laboratory to identify 1) whether the ammonia level was falsely elevated due to pre-analytical and/or analytical problems, or 2) whether the discrepancy was related to the patient's underlying arginase deficiency.

Case description

The patient is a fourteen-year-old male with arginase deficiency diagnosed at three years of age based on reduced arginase activity in red blood cells (November 2000). The patient had a history of severe intellectual disability, seizure disorder, asthma, gastrointestinal complications, and spastic diparesis.

The patient was put on a protein-restricted diet (December 2000) soon after diagnosis. His most recent diet is composed of 0.4 g/kg of essential amino acids from medical food (formula), and 0.4 g/kg of intact protein from food. If he doesn't eat his full-recommended amount of protein, it is given as Lactaid milk through the gastrostomy tube (G-tube). The mother keeps detailed food records and typical foods include Cheese Nips, Cheez-Its, Wise onion rings, Light & Lively yogurt, Pringles, low protein cheese, and animal crackers. His height (by the age of 14) was 160.3 cm (29th percentile for age, z-score 0.55), weight is 63.6 kg (85th percentile for age, z-score 1.02), and body mass index is 24.8 kg/m^2 (93rd percentile for age, z-score 1.44). Medications included sodium phenybutyrate (13.5 g/day), sodium benzoate (8.1 g/day), clonidine, speridone, Topamax, clinazepam, trazadine, Miralax, and Prilosec. The patient is generally well when there is no hyperammonemia. However, his baseline is that of severe developmental disability, behavior problems and spastic diparesis.

He has had 19 hospitalizations with elevated ammonia (>47 μmol/L) since 2008 with most of them requiring hydration and Ammonul (see description below) therapy. Eleven of these visits showed peak ammonia levels of more than four times normal (188 μmol/L). The average peak ammonia was 224 μmol/L (standard deviation [SD] = 127 μmol/L). In the majority of these episodes, the clinical signs of hyperammonemia did not match the severity of his elevated plasma ammonia. In comparison, he had 11 hospital visits due to elevated ammonia between 2000 and 2008 and only three visits showed peak ammonia levels of two times normal (94 μmol/L) and none beyond four times normal (Fig. 2B). During this period, the average of his peak ammonia was 80 μmol/L with SD of 31 μmol/L.

One of his typical emergency visits is described below. The patient presented to the emergency room with lethargy, emesis, and parental concerns about an "impending" metabolic crisis. The patient had complained of increased fatigue for several days, according to his mother. He had refused to eat by mouth on the day of admission and had been given hypercaloric and protein-free formula through his G-tube. Laboratory data obtained upon arrival for this visit indicated his ammonia was 105 μmol/L. Later analysis of the admission sample found arginine was 384 μmol/L (RI: 31–124 μmol/L) and decreased values for threonine, serine, isoleucine, and leucine. Glutamic acid and glutamine were within the reference intervals and gamma-glutamyltransferase (GTT) was 16 IU/L

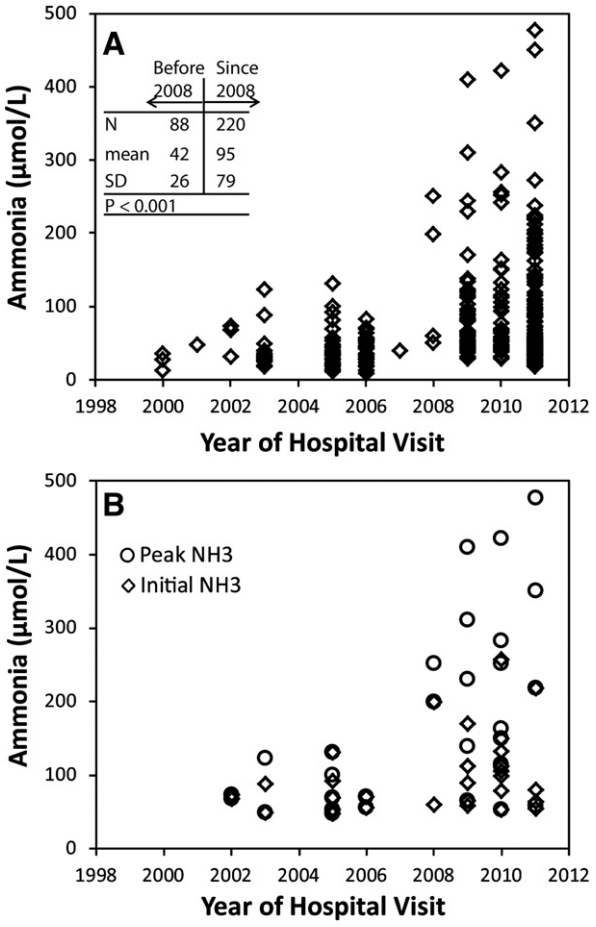

Fig. 2. A. All ammonia measurements from the patient between 2000 and 2011. The patient was diagnosed with arginase deficiency in 2000 nearly at age of three. The p value indicated the difference of ammonia measurements before and after 2008. B. The initial and peak ammonia levels for patient's hospital visits due to elevated ammonia. The open squares are for peak ammonia and the open diamonds are for initial ammonia. The p value indicated the difference of peak ammonia before and after 2008.