The First Neonatal Case of Neonatal Argininosuccinic Aciduria in Korea

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Case report

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Argininosuccinic aciduria (ASAuria) is a rare autosomal recessive urea cycle disorder. Neonatal presentation of ASAuria is the most common form. It is characterized by lethargy, feeding intolerance, decreased consciousness, and coma after 24 to 72 hours of birth. We describe a rare case of ASAuria in a female neonate who presented with severe hyperammonemia, a typical characteristic of urea cycle disorders. This patient’s diagnosis was confirmed by biochemical analyses, and we found that the patient had a point mutation of the argininosuccinate lyase gene, which was homozygous for a novel 556C>T substitution. We have never seen the neonatal form of ASAuria in Korea. Therefore, this is the first report of neonatal onset ASAuria in Korea.

Key Words: Argininosuccinic aciduria, Argininosuccinate lyase, Newborn

Introduction

Argininosuccinic aciduria is a rare autosomal recessive inborn error of the urea cycle, characterized by accumulation of argininosuccinic acid (ASA) in body fluids and hyperammonemia caused by argininosuccinate lyase (ASL) deficiency, the fourth enzyme in the urea cycle that catalyzes formation of arginine and fumarate from argininosuccinate. Patients with ASAuria are categorized into three clinical phenotypes according to deficient ASL activity: neonatal, infantile, and chronic form. Neonatal presentation of ASAuria, the most common form, is characterized by normal delivery followed by lethargy, feeding intolerance, decreased consciousness, and coma, usually occurring between 1 and 3 days, so most affected patients die undiagnosed. The infantile and chronic forms are characterized by mental retardation, intermittent ataxia, episodic hyperammonemia, and longer survival than the neonatal form.

ASAuria is rare in Asia, and no case has ever been reported in the newborn period in Korea. However, Ban et al.1) documented only anesthetic experience, not the process of diagnosing argininosuccinic acidemia. In addition, they mentioned at the beginning of their case report that the patient was diagnosed with urea cycle disorder at two years of age, so we guessed she was suspected of having late onset argininosuccinic acidemia. Although other urea cycle disorders, such as ornithine transcarbamylase deficiency and citrullinemia, have been reported2, 3), the neonatal form of ASAuria has not been reported.

We describe a case of neonatal onset ASAuria confirmed by biochemical analyses. This is the first report of a neonatal onset ASAuria (or ASL deficiency) in Korea.
Case report

A 3-day-old female neonate was transferred to Yeungnam University Hospital due to lethargy and hyperammonemia. She was born from the eighth pregnancy of healthy nonconsanguineous Korean parents. Their first three pregnancies were unsuccessful, and the fourth neonate had died of a severe intracranial hemorrhage at three days of age. The fifth and sixth pregnancies resulted in miscarriages. The seventh pregnancy was successful, delivering a healthy male baby. This female neonate was born at 38 weeks gestational age by normal spontaneous vaginal delivery. Her birth weight was 2,740 g, and Apgar scores were 9 at 1 minute and 10 at 5 minutes. The first two days after birth were uneventful. At the age of three days, she was admitted to a secondary care hospital due to vomiting and decreased sucking with weak physical movement. On admission, vital signs were as follows: 2,400 g of body weight, 170 beats/min of heart rate, 40 breaths/min respiratory rate and 74/44 mmHg of blood pressure. On physical examination, the baby did not react to any painful stimuli. The pupils were unresponsive, the corneal reflex was absent on both sides, and deep tendon reflexes were not observed. The anterior fontanelle was mildly distended. Upon admission, she had respiratory insufficiency and had developed cerebral edema and seizures. Markedly increased plasma ammonia levels were noted (24,561 μmol/L). Amino acid/acylcarnitine screening using tandem mass spectrometry (MS/MS) was performed. The results of MS/MS showed increased plasma levels of citrulline and ASA (semiquantitative value: 85.364 μM, normal range: 0.025–0.119). Plasma amino acid analysis using high performance liquid chromatography showed high citrulline levels and an ASA peak at 91.127 minutes but an undetectable arginine level (Fig. 1). Increased urinary excretion of citrulline was noted and ASA was detected on urinary amino acid analysis. Urinary organic acid analysis detected urinary excretion of orotic acid. Those findings were consistent with the acute stage of ASAuria. Electroencephalography showed continuous seizure activity with repetitive high-voltage spikes. We collected blood for DNA analysis from the patient and her older brother. Mutation analysis using PCR and direct sequencing of all exons and adjacent introns of the ASL gene were performed. Sequencing the ASL gene of the patient revealed homozygosity for a novel 556C>T substitution resulting in a mutation, which changed codon 186 of exon 7 in the ASL gene from arginine into tryptophan (R186W) (Fig. 2). The parents and brother had a Arg186Trp mutation in a heterozygous state in exon 7.

Peritoneal dialysis was initiated, and the ammonium concentration decreased to 288 μmol/L within 72 hours. Sodium butyrate (600 mg/kg per day) was supplemented in order to enhance ammonia excretion via urine. The patient’s seizures continued intermittently for 5 days despite

Fig. 1. Plasma amino acid chromatogram revealed an ASA peak at 91.127 minutes.
aggressive anticonvulsant therapy. The condition of the patient was improved, and she was started on nasogastric feeds after 11 days of treatment. On the 31st day in the hospital, she abruptly looked pale, and the blood counts showed a hemoglobin of 3.6 g/dL. A computed tomography of the head revealed a large ventricular hemorrhage with hydrocephalus. An external ventricular drainage was performed and she expired on the 47th hospital day.

Discussion

Disorders of the urea cycle are characterized by deficiency of an enzyme involved in the excretion of waste nitrogen. The prevalence of all urea cycle disorders is estimated as 1 in 30,000 live births. Inherited deficiencies have been observed for each of the five urea cycle enzymes: carbamoyl-phosphate synthase (CPS), ornithine transcarbamylase (OTC), argininosuccinate synthase (AS), ASL, and arginase. The clinical presentations of the deficiencies of CPS, OTC, AS, and ASL can be virtually identical, all being characterized by some degree of altered mental state and hyperammonemia. In the neonatal form of ASAuria, like other urea cycle disorders, an affected infant becomes symptomatic during the first few days of life, with signs and symptoms of hyperammonemia (refusal to eat, vomiting, lethargy, convulsion, and coma).

Transmitted as an autosomal recessive trait, ASAuria is caused by deficiency of ASL and was first recorded in the late 1950s. It is the most common inborn error of the urea cycle in Saudi Arabia, where it is likely a consequence of extensive consanguinity, but the overall incidence is rare. While there have been several cases of OTC and citrullinemia in urea cycle defects, no case of neonatal onset ASAuria has ever been reported in Korea.

This three day old newborn baby demonstrated a lethargic appearance and had severe hyperammonemia. The plasma amino acid analysis showed an increased level of citrulline and peak ASA. On the urinalysis, the citrulline level was mildly increased, and the ASA peak was found. Moreover, the glutamine level was increased, but the arginine level was decreased, and the orotic acid excretion was increased.

ASAuria is diagnosed by demonstrating markedly increased argininosuccinate in plasma and urine compared to other urea cycle disorders. In addition, urinary orotic acid is increased by shunting nitrogen waste from the urea cycle. Other abnormal plasma amino acid levels may be present, including low concentrations of arginine, or high concentrations of citrulline, but citrulline levels are less increased than that seen in citrullinemia. Although the level of ASA was not examined due to the lack of reagent, the diagnosis can be verified by the above laboratory findings.

This patient showed a significant homozygous mutation of the ASL gene, and her parents and brother were carriers of ASAuria.

The human ASL gene, located on chromosome 7cen-q11.27, is approximately 17 kb in length and composed of 17 exons. The presence of another partial sequence on chromosome 22 was assumed to be a pseudogene. The gene encodes for a 464-amino acid protein that catalyzes the degradation of argininosuccinate to fumarate and arginine. The sequence of ASL gene was cloned 25 years ago.
but the number of reported mutations is still small compared to other urea cycle defects, like ornithine transcarbamylase deficiency\textsuperscript{10}. Although mutations of the ASL gene were scattered throughout the gene, Trevisson et al. confirm that exon 7 seems to be a mutational hotspot\textsuperscript{12}. The mutation of position 556 (C→T) resulted in an amino acid exchange (p.Arg186Trp) affecting a conserved region of ASL that was nearly identical in monkeys and humans and may, therefore, cause defects in conserved function. This mutation was reported in an ASAuria patient, a compound heterozygote for the R186W and D115Y mutation by Imtiaz et al.\textsuperscript{4}. Therefore, we concluded that the neonate had ASAuria caused by a homozygous mutation of the ASL gene.

Molecular genetic studies are not essential for the diagnosis of ASAuria, because analysis of ammonia and argininosuccinic acid in plasma are sufficient to make a reliable diagnosis of the defect\textsuperscript{13}. However, genetic analysis should play an important role in the prenatal diagnosis of ASAuria. Although measurement of the ASL activity in chorionic villi is a reliable and sensitive method\textsuperscript{14}, it is complex and available in only very few laboratories worldwide. On the contrary, direct genetic analysis is feasible, fast, and specific and can be regarded as the method of choice for prenatal diagnosis. We therefore strongly recommended mutation testing to our ASA carrier parents in order to provide adequate prenatal counseling for her future pregnancies.

Management of ASAuria focuses on treatment of an acute hyperammonemia attack. Acute hyperammonemia should be treated promptly and vigorously. The goal of therapy is to remove ammonia from the body and to provide adequate calories and essential amino acids to halt further breakdown of endogenous protein.

This is the first case of the neonatal form of ASAuria in Korea, diagnosed by biochemical analyses and confirmed by sequencing the ASL gene that revealed the point mutation.

한글요약
ASAuria는 요소회로 이상증 중의 하나로 드물게 나타나는 상염색체 열성으로 유전되는 대사 질환이다. 체내에 ASA가 축적됨으로서 신생아 시기에 구토, 기면, 수유 곤란, 의식 장애를 보이며 적절한 조치를 하지 않으면 사망에 이르게 되는 치명적인 대사 질환이다. 이 질환은 혈중과 소변에 ASA가 증가하는 것으로 진단할 수 있다. 국내에서는 고전적 형태의 ASAuria가 아직 보고된 사례는 없으며, 이에 본 저자들은 고전적 ASAuria로 진단된 환아에서 유전자 검사를 통해 보인자 부모로부터 출생하였음을 진단한 신생아 환자 1예를 경험하였기에 보고하는 바이다.

References
