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ARTICLE

Low prevalence of argininosuccinate lyase deficiency among inherited urea cycle disorders in Korea

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Abstract

Argininosuccinic aciduria (ASA), which is considered to be the second most common urea cycle disorder (UCD), is caused by an argininosuccinate lyase deficiency and is biochemically characterized by elevation of argininosuccinic acid and arginine deficiency. In addition to hyperammonemia, other characteristic features of ASA include hepatic fibrosis, hypertension, neurocognitive deficiencies, and trichorrhexis nodosa. Herein, we retrospectively reviewed the clinical findings, biochemical profiles, and genotypic characteristics of five Korean patients with ASA, who showed typical phenotypes and biochemical findings of the disease. Molecular analysis of these patients revealed six novel *ASL* mutations. Next, we investigated the prevalence of all types of UCDs in Korea. Of note, over a two decade periods, ASA was only detected in 6.3% of patients with a UCD, which made it the fourth most common UCD in Korea. In comparison with Caucasians, in whom ASA is the second most common UCD, ASA is comparatively rare in East Asian populations, including Japanese and Koreans. These findings suggest the possibility of geographic variation in UCDs among ethnic groups.

Introduction

Argininosuccinic aciduria (ASA, OMIM #207900) is a urea cycle disorder (UCD) caused by a deficiency in aginino-succinate lyase (ASL). ASA is inherited in an autosomal recessive manner, and its incidence rate is estimated at 1:70,000 live births. ASA is the second most common UCD worldwide [1]. In Korea, more than 80% of newborns are screened for inherited metabolic disorders as part of the newborn screening program by tandem mass spectrometry [2]. An elevation of citrulline at newborn screening suggests that the baby might be affected by citrullinemia type 1 (CTLN1), ASA, or citrullinemia type 2 (CTLN2; citrin deficiency), further biochemical, molecular, and/or enzymatic testing is required for confirmatory diagnosis [3, 4]. The clinical manifestation of ASA is classified into two groups: a severe neonatal-onset form, presenting hyperammonemia within the first few days after birth and a late-onset form, with or without obvious episodic hyperammonemia. ASA is characterized by long-term complications, including chronic liver dysfunction, neurocognitive dysfunction, trichorrhexis nodosa, electrolyte imbalance, and hypertension [3]. Previously, our group reported various disease conditions as UCDs in Korea [5–8]. In this study, we reviewed the phenotypic, genotypic, and biochemical profiles and the treatment outcomes of ASA patients in Korea. We also determined the prevalence of ASA among inherited UCDs in Korea and compared these data to that in other populations.

Materials and methods

Patients

Five patients were included in our study. The diagnosis of ASA was based on biochemical findings and molecular analyses of the *ASL* gene (NM 000048). We retrospectively

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reviewed the clinical findings, including age at diagnosis, presenting symptoms, and developmental outcomes. In addition, biochemical findings, including plasma ammonia, plasma amino acid, and plasma and/or urine argininosuccinic acid levels were assessed. Written informed consent was obtained from all study subjects or their parents. The study protocol was approved by the Institutional Review Board of Asan Medical Center, Seoul, Korea.

Amino acid analysis

Serum urine and amino acid levels were analyzed by liquid chromatography-tandem mass spectrometry. An aliquot of 40 µL of the sample was added to 10 µL of 10% sulfosalicylic acid to precipitate proteins. After mixing and centrifugation (10,000×*g* for 2 min), the supernatant was mixed with 40 µL of borate buffer. Next an aliquot of 10 µL of the obtained solution was derivatized with the reagents supplied in the aTRAQ Kit for Amino Acid Analysis (Sciex, Framingham, MA, USA). The samples labeled with aTRAQ reagent Δ8 were mixed with the internal standards prelabeled with aTRAQ reagent Δ0. The determination of free amino acid levels was conducted using an HPLC instrument 1200 Infinity (Agilent Technologies, Santa Clara, CA, USA) combined with a 3200 Q-TRAP mass spectrometer (Sciex) with an electrospray ionization source.

Molecular analysis of the *ASL* gene

Genomic DNA was extracted from peripheral blood leukocytes with the Gentra Puregene blood kit (Qiagen, Hilden, Germany). Direct sequencing of the *ASL* gene was performed using the extracted genomic DNA. All 17 coding exons and the exon–intron boundaries of the genes of interest were individually amplified by polymerase chain reaction (PCR) using primers designed from the flanking regions. Amplified PCR products were directly sequenced by using the BigDye Terminator v.3.1 Cycle Sequencing Kit and an ABI3130*x*1 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). A real-time genomic PCR assay was performed to identify the copy number of each *ASL* exon(s), using 16 sets of primer pairs. Each primer pair was designed to be located in each exon. We used genomic DNA from two normal females as controls, and real-time PCR analyses with each primer pair were repeated three times. *ASL* consists of 17 exons and coding region includes exons 2–17. Therefore, we used the 16 sets of primer pairs for PCR (Table 1).

Spectrum of UCDs in a South Korean population

Patients who were diagnosed with each UCD such as ASA, ornithine transcarbamylase (OTC) deficiency, CTLN1, carbamoyl phosphate synthetase1 (CPS1) deficiency, *N*-acetylglutamate synthase (NAGS) deficiency, hyperammonemia-hyperornithinemia-homocitrullinuria (HHH) syndrome, and argininemia, at Asan Medical Center, Seoul, Korea from January 1999 to December 2017, were included in the current study. The number of patients with each UCD was calculated.

Table 1 Sequences of primers used for PCR of the *ASL*

	Sense (5′–3′)	Antisense (5′–3′)
Exon 2	agcgcagtgcccagaact	actgctgggctccagatgat
Exon 3	gcccctgctaccatcagact	actgcactgtttgctcaggg
Exon 4	gtgcgcttccaggactcag	tcacatgctgtctgccaatg
Exon 5	gggtatggaggtaggttggc	cagcctgaggtctgtgacca
Exon 6	gggggcagttagagttctgc	ctctgcctcgatcctggagt
Exon 7	gctgcagcgtgacacttttt	gcaggacattgatccgctt
Exon 8	ttctgaggtgagccaggtga	attcaatggcttggtcgtca
Exon 9	tgtgtcagggctgcctgc	ttgatgacctcagtgcccat
Exon 10	ctgttgccccaccctgat	cccacccactttacccattt
Exon 11	atgaaaatttagccgggtcc	aggtctggcggaggggtg
Exon 12	gacgtggctgccttcctc	ccttgagggtcatcaggagc
Exon 13	ggcctctgggctgatggt	gccttccatgggaagaacac
Exon 14	cccttcctttgttggggtat	agcacacctctccttccctg
Exon 15	agtgagacagagccgagtgg	aagtgctgggattacagggg
Exon 16	aaaaaggaaggggggtgcag	agatcacgtcgcccgaga
Exon 17	tcctaggaagtgagcctggg	agtccctgactgtccccact

Primers were designed with primer3 cgi v.3.0 served from Whitehead Institute (http://bioinfo.ut.ee/primer3-0.4.0/) using sequences from GenBank accession number of NT_007933.15

Results

Clinical features of ASA patients at presentation

Among the five included ASA patients (three males and two females, numbered 1–5), patients 1 and 2 had early onset ASA, which presented as hyperammonemic encephalopathy, whereas patients 3–5 had the late-onset form, which was identified by newborn screening (Table 2). Patient 1 manifested tachypnea and lethargy with hyperammonemia (344 µmol/L) and patient 2 developed comatose mentality and poor oral intake due to extremely high blood ammonia (988 µmol/L) a few days after birth. Patients 3–5 were given medical attention due to high blood citrulline levels at newborn screening, which was performed 2–3 days after birth. The ammonia levels of patients 3–5 were normal or only mildly elevated (45–104 µmol/L). Emergent management was required for patients 1 and 2, and they were administered intravenous sodium benzoate and oral phenylbutyrate and arginine to ameliorate hyperammonemia. Patient 2 required continuous venovenous hemodiafiltration

Table 2 Clinical characteristics of five patients with argininosuccinic aciduria

No.	Sex	Age at Dx[a] (months)	Symptoms at Dx	Initial laboratory findings										Outcome (at last follow-up)	
				NH_3 (μmol/L)	AST/ALT (IU/L)	Cr (mg/dL)	E′ imbalance	Amino acid analysis[b]						Age (year)	Symptoms
								Citrulline[c]	Glutamine[c] (μmol/L)	Glutamate[c] (μmol/L)	Arginine[c] (μmol/L)	Argininosuccinate			
												Serum (μmol/L)	Urine (μmol/g creatinine)		
1	F	<1	Seizure, coma, hepatomegaly, and trichorrhexis nodosa	344	29/53	0.4	—	289	1668	369	28	2762	27,7246	7	Neurocognitive deficiency Hepatomegaly
2	M	<1	Poor oral intake, lethargy, hepatomegaly, and trichorrhexis nodosa	988	30/51	0.4	+[d]	3491	1686	2360	180	Detect[e]	22,229	6	Neurocognitive deficiency Hepatomegaly Electrolyte imbalance
3	M	1	—	104	53/30	0.46	—	115	505	63	110	25408	13467[f]	3	—
4	F	1	Trichorrhexis nodosa	45	34/18	0.25	—	455	907	75	118	Detect[e]	64076	2	Neurocognitive deficiency
5	M	16[g]	—	53	42/24	0.37	—	190	257	83	60	–[g]	ND[h]	4	—

[a] Age at diagnosis is consistent with the time of amino acid analysis performed except in patient 5

[b] Amino acid analyses were performed by LC-MS/MS method

[c] Normal ranges of amino acids: citrulline, 10–45 μmol/L; glutamine, 376–709 μmol/L; glutamate, 62–620 μmol/L; arginine, 6–140 μmol/L

[d] Hypokalemia, serum potassium 1.9 mmol/L (TTKG 17.19)

[e] The exact value of serum argininosuccinate was not available

[f] μmol/L

[g] One year later, serum argininosuccinate was detected, but the exact value of arginosuccinate was not available

[h] ND, not determined

Table 3 Molecular findings of five patients with argininosuccinic aciduria

Patient No.	Patient *ASL* genotype	Family	
		Father	Mother
1	c.[545G>A];[557G>A] (p.[Arg182Gln];[Arg186Gln])	c.[545G>A];[=] (p.[Arg182Gln];[=])	c.[557G>A] (p.[Arg186Gln])
2	**c.[861G>T];[1256del] (p.[Lys287Asn];[Leu419Argfs*6])**	c.[861G>T];[=] (p.[Lys287Ans];[=])	c.[1256del];[=] (p.[Leu419Argfs*6];[=])
3	**c.[411G>A];[1124A>G] (p.[Trp137*];p[Tyr375Cys])**	ND	
4	**c.[467C>T];**[1144-?1250+?del] (**p.[Pro156Leu];**?)	ND	
5	**c.[467C>T];[467C>T] (p.[Pro156Leu];[Pro156Leu])**	ND	

Bold characters, novel gene mutation

ASL argininosuccinate lyase, *ND* not determined

for 24 h to rapidly correct hyperammonemia. At diagnosis, patients 1 and 2 showed elevation of glutamine level, and normal range of arginine level. Also patient 1 showed elevation of glutamate level. Patients 3–5 showed normal range of glutamine, glutamate, and arginine (Table 2). Patients 1–4 showed elevated argininosuccinic acid levels in serum and, or urine (Table 2). Patient 5 had no elevation of argininosuccinic acid at initial serum amino acid analysis, but its elevation was detected for the first time at 16 months of age, although the exact value was not available. An electrolyte imbalance was noted in patient 2, who had hypokalemia with increased renal excretion (transtubular potassium gradient, 17.19).

Mutational analysis

A total of eight different mutations were identified in the 10 tested alleles (Table 3). Two mutations (p.Arg182Gln, p.Arg186Gln) were previously reported [9, 10], while the other six were novel mutations (p.Lys287Asn, p.Leu419Argfs*6, p.Trp137*, p.Tyr375Cys, p.Pro156Leu, and an exon 15 deletion). One mutation, p.Pro156Leu was found in three alleles. According to the Genome Aggregation Database (gnomAD), the minor allele frequency of the c.467C>T (p.Pro156Leu) variant is 0.000008136. The p.Pro156Leu mutation was predicted to be pathogenic by several in silico prediction programs, including PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), Sorting Intolerant From Tolerant (http://sift.jcvi.org/), and MutationTaster (http://www.mutationtaster.org/). Two other novel mutations, p.Lys287Asn and p.Tyr375Cys, were not observed in the control population by gnomAD (http://gnomad.broadinstitute.org/), ExAc (http://exac.broadinstitute.org/), KRGDB (http://152.99.75.168/KRGDB/menuPages/intro.jsp/), and were also predicted to be pathogenic by in silico prediction programs. p.Leu419Argfs*6 and p.Trp137* were novel frameshift and nonsense mutations. Exon 15 deletion was detected by genomic real-time PCR analysis.

Clinical courses of the ASA patients

All five patients have continued maintenance therapy. They have been managed with a protein-restricted diet (1.0–1.5 g/kg/day) and arginine supplementation (100–150 mg/kg/day). Plasma levels were monitored on a regular basis. In addition, phenylbutyrate (100–200 mg/kg/day) and sodium benzoate (100–150 mg/kg/day) were administered to prevent hyperammonemic episodes. Under close clinical observation, patient 3 was able to discontinue the nitrogen scavenging therapies without a hyperammonemic episode 3 years of age. The Korean Developmental Test for infants and toddlers was conducted for all patients [11]. In this test, a score of >80 in each of five domains including gross motor, fine motor, personal-social, language, and cognitive-adaptive skills indicates normal development. Patients 1 and 2 with neonatal-onset scored in the 50–60 s in all domains until the latest evaluation. Among patients with late-onset ASA (patients 3–5), only patient 4 had a score in the 60 s in fine motor skill and language development until 2 years of age. All five patients presented a normal range of AST/ALT level. Additionally, their abdominal ultrasonography findings were normal except in patients 1 and 2. Patients 1 and 2 developed hepatomegaly based on physical examination and ultrasonography. Patients 1, 3, and 4 had brittle, sparse hair. All patients had normal blood pressure during the 2–7 years of observation.

Spectrum of UCDs in a Korean population

Eighty patients were diagnosed with a UCD in the Medical Genetics Center of Asan Medical Center, Seoul, Korea, by biochemical and molecular analyses, during the period from January 1999 to December 2017. The entire spectrum of

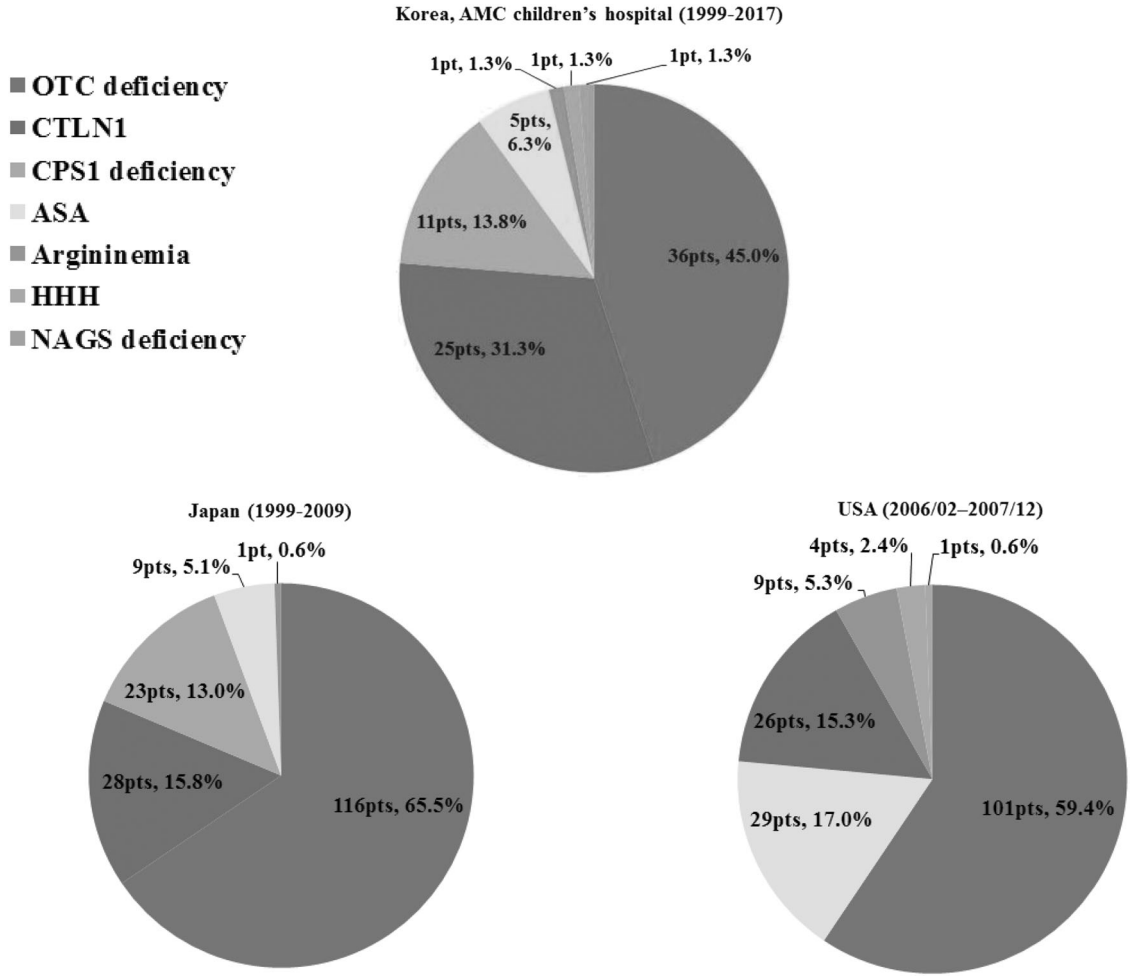

Fig. 1 The prevalence rates of inherited urea cycle disorders in Korea, Japan [27], and the United States of America [24]

UCDs diagnosed at our institution was evaluated to determine the prevalence in our UCD cohort, and only five patients were diagnosed with ASA. The most common disorder was OTC deficiency (36 patients, 45.0%), and the second and third most common UCDs were CTLN1 (25 patients, 31.3%) and CPS1 deficiency (11 patients, 13.8%), respectively. In contrast, only 5 patients (6.3%) were diagnosed with ASA, while 1.3% (each) were diagnosed with argininemia, HHH, and NAGS deficiency (Fig. 1).

Discussion

The current study is the first to describe the clinical and molecular characteristics of ASA patients in a Korean population. The five patients described here showed the typical phenotypes and biochemical characteristics of ASA. Two patients were affected with neonatal-onset severe ASA, while the remaining three patients had less severe late-onset ASA. The distinct clinical features of ASA have been described as a constellation of phenotypes, including trichorrhexis nodosa, electrolyte imbalance (hypokalemia), hypertension, hepatic disease, and neurocognitive deficiency. Neurodevelopmental delay is also found in other UCDs, but is more common in patients with ASA [3]. Hair is composed of 10.5% arginine by weight, thus the insufficient arginine of the patients with ASA results in weak hair shaft [12]. In this study, three patients presented trichorrhexis nodosa, which was improved with arginine supplementation. The mechanism of hypokalemia in ASA is unclear; however, increased renal loss may be involved [3]. In our study, one patient has presented hypokalemia with increased renal potassium excretion. The severity of hepatic dysfunction in ASA is variable, ranging from hepatomegaly to liver cirrhosis. The hepatic disease is considered to be progressive [13–16], and hepatic fibrosis is often associated in children with neonatal-onset ASA [17, 18]. Although, there were only two patients with hepatomegaly in our study, based on short-term follow-up period for each patient, life-long monitoring is needed. Neurocognitive

deficits are often observed more frequently in patients with neonatal-onset ASA than in patients with late-onset ASA, as was also observed for our patients. Neurological developmental delay is associated with the ammonia level in a hyperammonemic episode, the glutamine level, and the duration of hyperammonemic exposure. Thus, early identification and intervention are very important to improve neurological outcomes. Although, late-onset ASA patients may never have a hyperammonemic events, like patient 4 [19], neurocognitive deficits can still develop. Therefore, long-term observation for neurocognitive deficits is required in all patients with ASA, and early intervention is required to minimize these deficits. All patients with ASA in Korea receive arginine supplementation, are put on a protein-restricted diet and are treated with ammonia scavengers. Although, sodium nitrite is not yet available in Korea, sodium nitrite therapy is expected to become a standard treatment for ASA in the near future to help prevent long-term complications [15, 20, 21]. On a molecular level, it is notable that six out of the seven *ASL* mutations identified in the five patients were novel and that p.Pro156Leu was present in three alleles of two unrelated patients. Two mutations in our ASA patients, p.Arg182Gln and p.Arg186Gln, were previously reported in Dutch and Italian patients, respectively [9, 10]. In Caucasians, p.Arg385Cys, p.Gln116Ter, p.Arg12Gln, p.Ile100Thr, p.Arg186Trp, p.Glu189Gly, p.Gln286Arg, and p.Val178Met are common mutations [10, 22, 23], but are not found in Korea. Unfortunately, we could not find an appropriate article describing the *ASL* mutation spectrum in Japan or other Asian countries. Additional studies are needed to characterize the molecular genetic features of ASA among different ethnicities. As a major tertiary medical center in Korea, our center has been taking care of most of UCD patients in Korea [5–8], therefore, the proportions of each UCD diagnosed in our center likely represent the spectrum of UCDs in Korea. When we compared the relative prevalence of each UCD in Korea to those in Japan, the USA, and European countries, a difference was observed among these populations (Fig. 1). OTC deficiency was the most common phenotype worldwide. However, ASA is the second most common inherited UCD in the USA and European countries [14, 24, 25], whereas ASA was as rare as 5.1–5.6% in Japan and 6.3% in Korea, making it the fourth most common UCD in these East Asian countries [26, 27]. We also investigated the spectrum of UCDs in other East Asian countries, including China and Taiwan. Although, there were no epidemiological surveys of UCDs, ASA is expected to be extremely rare in these countries as well [28, 29]. In contrast, ASA was the most common UCD in Malaysia [30, 31]. These findings suggest that there might exist the ethnic differences in the prevalence rates of each UCD among various populations. In conclusion, ASA is expected to be rare in the perspective of the UCD spectrum in East Asian countries, suggesting geographic variation in UCDs among ethnic groups. Further studies are required to identify more cases in diverse populations to understand the clinical and molecular spectrum of ASAs and share the clinical experiences to develop new treatment strategies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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