Physical, cognitive, and social status of patients with urea cycle disorders in Japan

Jun Kido [a],[*], Shirou Matsumoto [a], Tetsuya Ito [b], Shinichi Hirose [c], Kaori Fukui [d], Kanako Kojima-Ishii [e], Yuichi Mushimoto [e], Shinobu Yoshida [f], Mika Ishige [g], Norio Sakai [h], Kimitoshi Nakamura [a]

[a] Department of Pediatrics, Graduate School of Medical Sciences, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan
[b] Department of Pediatrics, Fujita Health University School of Medicine, Toyoake, Japan
[c] Department of Pediatrics, School of Medicine, Fukuoka University, Fukuoka, Japan
[d] The Department of Pediatrics and Child Health, Kurume University School of Medicine, Kurume, Japan
[e] Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[f] Department of Pediatrics, Omihachiman Community Medical Center, Shiga, Japan
[g] Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo, Japan
[h] Child Healthcare and Genetic Science Laboratory, Division of Health Sciences, Osaka University Graduate School of Medicine, Suita, Japan

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ABSTRACT

Urea cycle disorders (UCDs) are inherited metabolic diseases that lead to hyperammonemia. Severe hyperammonemia adversely affects the brain. Therefore, we conducted a nationwide study between January 2000 and March 2018 to understand the present status of UCD patients in Japan regarding diagnosis, treatments, and outcomes. A total of 229 patients with UCDs (126 patients: ornithine transcarbamylase deficiency [OTCD]; 33: carbamoyl phosphate synthetase 1 deficiency [CPS1D]; 48: argininosuccinate synthetase deficiency [ASSD]; 14: argininosuccinate lyase deficiency [ASLD]; and 8: arginase 1 deficiency [ARG1D]) were enrolled in the present study. Although growth impairment is common in patients with UCDs, we discovered that Japanese patients with UCDs were only slightly shorter than the mean height of the general adult population in Japan. Patients with neonatal-onset UCDs are more likely to experience difficulty finding employment and a spouse; however, some patients with late-onset UCDs were employed and married. Additionally, intellectual and developmental disabilities, such as attention deficit hyperactivity disorder (ADHD) and autism, hinder patients with UCDs from achieving a healthy social life. Moreover, we identified that it is vital for patients with UCDs presenting with mild to moderate intellectual disabilities to receive social support. Therefore, we believe the more robust social support system for patients with UCDs may enable them to actively participate in society.

1. Introduction

The urea cycle comprises mitochondrial enzymes, including *N*-acetylglutamate synthase (NAGS; EC 2.3.1.1), carbamoyl phosphate synthetase 1 (CPS1; EC 6.3.5.5), and ornithine transcarbamylase (OTC; EC 2.1.3.3), as well as cytoplasmic enzymes, including argininosuccinate synthetase (ASS; EC 6.3.4.5), argininosuccinate lyase (ASL; EC 4.3.2.1), and arginase 1 (ARG1; EC 3.5.3.1). This cycle contributes to the elimination of excess endogenous and exogenous nitrogen from the living body by transforming ammonia into urea. Urea cycle disorders (UCDs), with an estimated prevalence of 1 per 50,000 live births in Japan, are

inherited metabolic diseases that cause hyperammonemia [1]. The clinical manifestations of UCDs are variable. The most severe type is neonatal-onset UCD, which occurs within 28 days after birth [2] and is characterized by vomiting, food refusal, lethargy, tachypnea, impaired consciousness, and multiorgan failure [3]. Patients with neonatal-onset UCD often experience recurrent hyperammonemic attacks and have a poor neurodevelopmental prognosis [2]. Late-onset UCDs, the milder type, can develop at any age beyond 28 days old and are characterized by hyperammonemic attacks triggered by stress, such as infection, vomiting, and surgery. More insidious symptoms include failure to thrive, liver disorders, behavioral disorders, psychiatric symptoms, and

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developmental delays [4–6].

A low-protein diet including a special formula and alternative pathway therapies, such as sodium benzoate and sodium phenylbutyrate, are essential in treating patients with UCD [7–9]. Arginine is a significantly important treatment for patients with UCDs except those with ARG1 deficiency (ARG1D) because their bodies exhibit a shortage of arginine [10]. Citrulline is often administered to patients with OTC deficiency (OTCD) and CPS1 deficiency (CPS1D) because it is lacking in these patients and is converted to arginine in the urea cycle [11,12]. Additionally, patients with UCDs receiving enhanced protein restriction therapy may require L-carnitine and essential amino acid supplements [13,14]. In patients with severe hyperammonemia and hepatic coma, hemodialysis is an effective treatment for rapidly reducing blood ammonia levels [15–17]. In severe cases, liver transplantation (LT) is performed to manage the pathogenesis of UCDs, prevent recurrent hyperammonemic attacks, and improve the quality of life of patients [18].

We previously evaluated the long-term outcomes and clinical manifestations of patients with UCD by conducting a nationwide study in Japan [2,4,19,20]. Almost 10 years have passed since the previous study was performed, and medical technology and emergency transport technology in Japan have improved since then. For example, sodium phenylbutyrate has since been approved as a UCD treatment by health insurance, and L-citrulline supplements are supplied to UCD patients by the Japanese Society for Inherited Metabolic Diseases [12]. Moreover, guidelines for the diagnosis and treatment of UCDs have been created in Japan; therefore, clinicians now have a deeper understanding of UCDs. In recent years, conventional assessments of intelligence, developmental disabilities, psychiatric disorders, including attention deficit hyperactivity disorder (ADHD), and learning disabilities have been conducted in patients with UCDs from various countries [21–25]. However, a deeper understanding of environmental factors and the social status, including social support networks, of patients with UCDs is required. Therefore, in the present study, we performed a nationwide study in Japan to better understand the current physical, cognitive, and social status of patients with UCDs. Herein, we identified novel challenges based on the clinical outcomes of patients with UCDs and discuss shortfalls to be addressed in future research studies.

2. Materials and methods

2.1. Study participants

In 2018, we invited 1009 medical institutions, including the respective departments of pediatrics, endocrinology and metabolism, neonatology, genetics, and transplant surgery, to participate in a questionnaire survey regarding patients with UCDs (Supplemental data 1). Each institution was a medical center that serviced a local area in Japan and had approximately 300 beds, based on previous survey reports [4]. The questionnaire aimed to establish whether doctors had diagnosed or provided medical treatment to patients with UCDs, including OTCD, CPS1D, NAGS deficiency (NAGSD), ASS deficiency (ASSD), ASL deficiency (ASLD), and ARG1D. Of the 1009 institutions, 731 (72%) responded, and 148 confirmed that patients with UCDs had been diagnosed and/or treated at their facility. Thereafter, in 2019, we delivered a second questionnaire survey to these 148 institutions, and 110 (74%) responded. As of 2020, we acquired the clinical data of 229 patients with UCDs from clinicians working at these institutions who had diagnosed and/or treated patients with UCDs between January 2000 and March 2018.

The clinical data of the 229 patients with UCDs were then analyzed. A patient who visited several institutions was regarded as a single patient. The 229 patients with UCDs (CPS1D, OTCD, ASSD, ASLD, and ARG1D) were diagnosed based on clinical manifestations, family history, enzyme activity, metabolite analysis (blood amino acid levels and urinary levels of orotic acid), and/or DNA analysis.

Physical manifestations of UCDs were assessed and recorded by the clinicians who had diagnosed and/or treated patients. Visual impairment was defined as visual acuity of 20/200 or less in the naked-eye visual acuity test. Auditory impairment was regarded as hearing loss of 60 or more decibels in the unilateral ear. Intellectual assessments were performed by clinical psychologists, pediatricians, and/or child psychiatrists using standardized tests, such as the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), Wechsler Intelligence Scale for Children (WISC), Wechsler Adult Intelligence Scale (WAIS), Kaufman Assessment Battery for Children, Illinois Test of Psycholinguistic Abilities, and/or Enjoji Scale of Infant Analytical Development. Developmental assessments were performed according to diagnostic criteria of the International Statistical Classification of Diseases and Related Health Problems (ICD)-10 or Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V), as well as the Modified Checklist for Autism in Toddlers, Social Responsiveness Scale, Autism Diagnostic Interview-Revised, Childhood Autistic Rating Scale-Second Edition, ADHD Rating Scale-IV, Conners' Adult ADHD Diagnostic Interview for DSM-IV, Conners' Adult ADHD Rating Scales, and Learning Disabilities Inventory-Revised.

This study was approved by the ethics committee of the Faculty of Life Science, Kumamoto University, Japan. Informed consent was obtained from the patients or their parents.

2.2. Statistical analysis

One-way analysis of variance (ANOVA) was performed using GraphPad Prism 8.0 (GraphPad Software, San Diego, California, United States of America) to compare plasma amino acid levels between groups. Moreover, the association between height and plasma levels of valine (Val), leucine (Leu), and isoleucine (Ile) were investigated using multivariable analysis, including multiple linear regression and logistic regression analysis. P values of <0.05 were considered statistically significant.

3. Results

A total of 229 patients with UCDs (73 male patients with OTCD, median age 16 years 2 months (interquartile range [IQR]: 10 years 3 months–28 years 10 months); 53 female patients with OTCD, median age 11 years 4 months (IQR: 6 years 4 months–19 years 1 month); 33 CPS1D patients (male: 11, female: 22), median age 9 years 4 months (IQR: 5 years–15 years 7 months); 48 ASSD patients (male: 22, female: 26), median age 11 years 4 months (IQR: 5 years 5 months–17 years 3 months); 14 ASLD patients (male: 9, female: 5), median age 23 years 4 months (IQR: 13 years 10 months–30 years 3 months); and 8 ARG1D patients (male: 4, female: 4), median age 21 years 8 months (IQR: 13 years 5 months–37 years 6 months)) were enrolled in the present study (Supplemental data 1). No patients in the present study had NAGSD. Of the 229 patients, 76 patients (OTCD: 30 males and 14 females; CPS1D: 21; ASSD: 10; and ARG1D: 1) had undergone living donor LT, including carrier donors. Thirty-eight patients (50%) underwent LT within 1 year of age. Fifty-two patients were neonatal-onset UCDs (OTCD: 23 males; CPS1D: 19; and ASSD: 10), and 38 patients with neonatal-onset UCDs (OTCD: 19 males; CPS1D: 16; and ASSD: 3) received LT by 1 year of age; 3 male patients with OTCD underwent LT within 3 months of age. Most patients with neonatal-onset UCDs had undergone LT to prevent hospitalization and ameliorate their quality of life because of frequent and recurrent hyperammonemic attacks after onset. Most patients with UCDs undergoing LT had not experienced recurrent hyperammonemic attack.

Table 1 indicates the frequency of physiognomy and physical manifestations in 215 patients with UCDs. Short stature was present in 33% (70/215) of the patients, low weight gain in 23% (50/215), hepatomegaly in 12% (26/215), spleen enlargement in 1% (2/215), pili torti (twisted hair) in 4% (9/215), spasticity in 8% (17/215), and athetosis in

Table 1
Physiognomy and physical manifestations in patients with urea cycle disorders (UCDs)[a].

	Short stature	Poor weight gain	Hepatomegaly	Spleen enlargement	Pili torti (Twisted hair)	Spasticity	Athetosis
Neonatal-onset OTCD (N = 34)	41% (14/34)	41% (14/34)	12% (4/34)	0% (0/34)	0% (0/34)	18% (6/34)	3% (1/34)
Late-onset OTCD (N = 83)	18% (15/83)	8% (7/83)	8% (7/83)	0% (0/83)	1% (1/83)	4% (3/83)	2% (2/83)
CPS1D (N = 33)	52% (17/33)	39% (13/33)	12% (4/33)	0% (0/33)	0% (0/33)	9% (3/33)	6% (2/33)
ASSD (N = 43)	35% (15/43)	21% (9/43)	7% (3/43)	0% (0/43)	7% (3/43)	2% (1/43)	2% (1/43)
ASLD (N = 14)	21% (3/14)	21% (3/14)	50% (7/14)	14% (2/14)	36% (5/14)	7% (1/14)	0% (0/14)
ARG1D (N = 8)	75% (6/8)	50% (4/8)	13% (1/8)	0% (0/8)	0% (0/8)	38% (3/8)	0% (0/8)
Total (N = 215)	33% (70/215)	23% (50/215)	12% (26/215)	1% (2/215)	4% (9/215)	8% (17/215)	3% (6/215)

[a] Abbreviations: OTCD, ornithine transcarbamylase deficiency; CPS1D, carbamoyl phosphate synthetase 1 deficiency; ASSD, argininosuccinate synthetase deficiency; ASLD, argininosuccinate lyase deficiency; ARG1D, arginase 1 deficiency.

3% (6/215) of the patients. In neonatal-onset OTCD, short stature was present in 41% (14/34) of the patients, low weight gain in 41% (14/34), hepatomegaly in 12% (4/34), spasticity in 18% (6/34), and athetosis in 3% (1/34) of the patients. We identified that short stature was a common manifestation in patients with UCDs. Conversely, hepatomegaly and pili torti (twisted hair) were manifestations more specific to patients with ASLD.

Fig. 1 presents the height of male and female patients with UCDs. In male OTCD patients, the height of 33% (15/45) of patients aged <17 years and 12% (2/17) of patients aged ≥17 years was below the third percentile (Fig. 1A). In female OTCD patients, the height of 27% (6/22) of patients aged <17 years and 32% (9/28) of patients aged ≥17 years was below the third percentile (Fig. 1B). Moreover, the height of 33% (3/9) of male CPS1D patients (Fig. 1C), 19% (4/21) of male ASSD patients (Fig. 1E), and 38% (3/8) of male ASLD patients (Fig. 1G) was below the third percentile. Whereas the height of 43% (9/21) of female CPS1D patients (Fig. 1D), 27% (6/22) of female ASSD patients (Fig. 1F), and 20% (1/5) of female ASLD patients (Fig. 1H) was below the third percentile.

In patients aged ≥17 years, the median height of male OTCD (n = 17), male ASSD (n = 6), male ASLD (n = 4), and male ARG1D patients (n = 3) was 168.3 (IQR: 165.2–170.2), 159.1 (157.8–159.8), 163.2 (154.2–170.6), and 146.4 cm (145.2–148.4), respectively. The median height of female OTCD (n = 26), female CPS1D (n = 7), female ASSD (n = 6), and female ASLD (n = 3) patients aged ≥17 years was 153.5 (IQR: 147.5–156.3), 147.0 (144.6–150.8), 149.5 (146.0–155.0), and 150.0 cm (149.6–151.0), respectively. In 2018, the median height of 17-year-old Japanese males and females was 170 cm (IQR: 166–174) and 157 cm (IQR: 154–161), respectively (https://www.mext.go.jp/component/b_menu/other/__icsFiles/afieldfile/2019/03/25/1411703_03.pdf).

Table 2 indicates the frequency of psychoneurotic and psychological manifestations in patients with UCDs. We identified that hypoglycemia (< 60 mg/dL) was present in 8% (18/215) of the patients, hyperammonemia (> 60 µmol/L) in 92% (198/215), hyperammonemic coma in 66% (141/215), convulsion in 41% (88/215), impaired intelligence in 48% (103/215), cerebral palsy in 22% (48/215), hypertonia in 12% (26/215), hypotonia in 10% (22/215), muscle weakness in 14% (31/215), skeletal muscle atrophy in 9% (19/215), a visual impairment in 5% (10/215), auditory impairment in 2% (5/215), abnormal magnetic resonance imaging (MRI) or computerized tomography (CT) findings in 35% (76/215), and abnormal brain waves in 26% (56/215) of the patients. Moreover, autism was diagnosed in 5% (11/215) of UCD patients, ADHD in 5% (10/215), an adjustment disorder in 5% (10/215), a learning disorder in 11% (24/215), communication disorder in 7% (16/215), and mood disorder in 2% (4/215) (Table 2B). Supplemental data 2 showed the rate of developmental disabilities in patients with UCDs who received a developmental assessment. The adaptive and behavioral profiles of patients with UCDs were not as impaired as their intellectual abilities.

Table 3 demonstrates the frequency of gastrointestinal and hematological manifestations in patients with UCDs. Aversion to protein was present in 17% (36/215) of UCD patients, poor appetite in 22% (47/215), nausea or vomiting in 45% (97/215), diarrhea in 3% (7/215), elevated transaminase levels (aspartate transaminase [AST] and alanine transaminase [ALT] > 100 IU/L) in 41% (88/215), leukopenia (< 4000/µL) in 7% (16/215), anemia (< 10 g/dL) in 16% (35/215), thrombocytopenia (< 10 × 10^4/µL) in 11% (24/215), and bleeding or thrombotic events, such as stroke, gastrointestinal bleeding, and vascular thrombosis, in 7% (15/215) of the patients.

Moreover, we evaluated the employment, marital, and parturition status of UCD patients ≥18 years of age. Of the 6 patients with neonatal-onset OTCD (male: 4; female: 2) ≥ 18 years of age, none had been employed, married, or given birth. Regarding the 45 patients with late-onset OTCD (male: 19; female: 26) ≥ 18 years old, 31 patients had been employed, 11 were married, and 7 had experienced childbirth. Additionally, 2 male patients and 1 female patient had received LT.

Of the 6 patients with CPS1D (male: 1; female: 5), 3 patients who underwent LT had been employed, and 1 female patient who also received LT was married and experienced childbirth. The latter patient experienced hyperammonemia at the age of 58. Regarding the 11 patients with ASSD (male: 5; female: 6) ≥ 18 years of age, 8 patients had been employed, but none were married or had given birth. Moreover, only 1 male patient had undergone LT. Of the 9 patients with ASLD (male: 6; female: 3) ≥ 18 years old, 4 patients with mental retardation had been employed, but none were married or experienced childbirth. Furthermore, none of the 4 patients with ASLD (male: 3; female: 1) ≥ 18 years of age had been employed or married.

Table 4A presents the plasma amino acid levels of patients with UCDs at disease onset or time of diagnosis. The median plasma citrulline (Cit) levels at the time of onset or diagnosis was 3.9 µmol/L (IQR: 1.2–5.5) in neonatal-onset OTCD patients (n = 28), 13.9 µmol/L (IQR: 8.1–-19.2) in late-onset OTCD patients (n = 65), not detectable (ND) (IQR: ND–4.3 µmol/L) in CPS1D patients (n = 24), 2120 µmol/L (IQR: 1075–2856) in ASSD patients (n = 41), 230.7 µmol/L (IQR: 188.1–397.2) in ASLD patients (n = 12), and 30.0 µmol/L (IQR: 21.5–46.6) in ARG1D patients (n = 8). We observed that plasma Cit levels were considerably lower in patients with neonatal-onset OTCD and CPS1D, reduced in late-onset OTCD patients, and elevated in patients with ASSD and ASLD compared to reference levels. Moreover, we identified that plasma arginine (Arg) levels were elevated in patients with ARG1D. Thereafter, we evaluated the plasma levels of branched-chain amino acids (BCAAs) in patients with UCDs receiving treatment, such as protein restriction
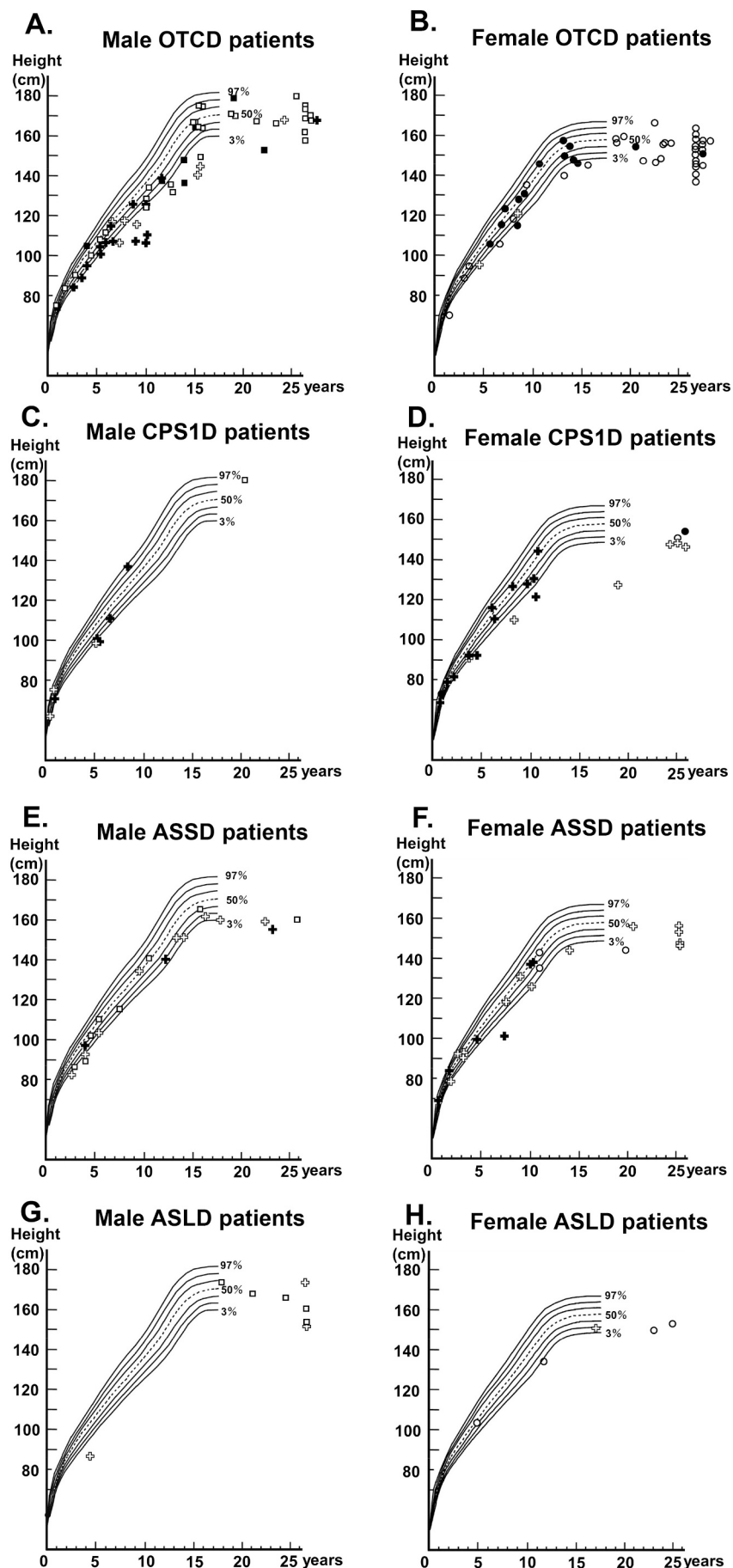
Fig. 1. The height of patients with urea cycle disorders (UCDs).

A. Male patients with ornithine transcarbamylase deficiency (OTCD; *n* = 62).

B. Female patients with OTCN (*n* = 50).

C. Male patients with carbamoyl phosphate synthetase 1 deficiency (CPS1D; *n* = 9).

D. Female patients with CPS1D (*n* = 21).

E. Male patients with argininosuccinate synthetase deficiency (ASSD; *n* = 20).

F. Female patients with ASSD (*n* = 22).

G. Male patients with argininosuccinate lyase deficiency (ASLD; *n* = 8).

H. Female patients with ASLD (*n* = 5).

□: Late-onset in male patients without liver transplantation (LT).

■: Late-onset in male patients with LT.

○: Late-onset in female patients without LT.

●: Late-onset in female patients with LT.

✢: Neonatal-onset without LT.

✚: Neonatal-onset with LT.

and medications (Table 4B). Plasma Val and Leu levels were lower in patients with CPS1D, ASLD, and ARG1D compared to reference levels. Additionally, plasma Ile levels were reduced in patients with all types of UCDs. However, one-way ANOVA detected no significant differences between patients with different UCDs relative to plasma levels of Val, Leu, and Ile ($P > 0.05$). We analyzed the association between height and plasma BCAA levels in UCD patients aged $\geq$17 years using multivariable analysis, including multiple linear regression and logistic regression analysis. However, none of the plasma amino acids were associated with height when evaluating all UCDs collectively as well as each UCD separately (neonatal-onset OTCD [$n = 1$], late-onset OTCD [$n = 41$], CPS1D [$n = 5$], ASSD [$n = 10$], ASLD [$n = 8$], and ARG1D [$n = 4$]) ($P > 0.05$).

4. Discussion

In the present study, we evaluated the clinical manifestations in Japanese patients with UCDs. Clinical manifestations of UCDs have been reported by clinicians, including members of the European registry and network for Intoxication type Metabolic Disease (E-IMD) and the UCD consortium in the USA [5–7,23–25].

This study suggested that many patients with neonatal-onset OTCD, CPS1D, and ARG1D suffered from growth impairment, including short stature and poor weight gain. Additionally, numerous patients with ASLD presented with hepatomegaly and pili torti (abnormal twisted hair). Trichorrhexis nodosa is characterized by nodular swelling of the hair shaft accompanied by frayed fibers and cuticle loss. Approximately 50% of patients with ASLD develop hair abnormalities that manifest as dull, brittle hair surrounded by partial alopecia areas [26]. Moreover, liver lesions and elevated liver enzyme levels were detected in almost 50% of patients with ASLD [6,27–29]. Similarly, many Japanese patients with ASLD presented with liver complications. The mechanisms underlying liver involvement in ASLD are not clearly understood, although argininosuccinic acid and ammonia are toxic to hepatocytes. Moreover, imbalanced levels of arginine in the body may have adverse effects on hepatocytes. A lack of arginine leads to decreased nitric oxide (NO) synthesis [30], potentially resulting in excessive oxidative stress and liver cirrhosis. Persico et al. [31] suggested that endothelial NO synthase dysfunction may be crucial in the pathogenesis of non-alcoholic steatohepatitis and liver disease progression, increase in vascular resistance linked to portal hypertension and fibrosis. Excess arginine results in increased levels of argininosuccinic acid. Taken together, arginine, leucine, and glutamine may affect cell growth, autophagy, and protein synthesis via rapamycin complex 1 (mTORC1) [32].

Symptomatic UCD patients, particularly those with early-onset UCDs, present progressive growth impairment over time [19,33]. Of note, the restriction of protein intake was related to growth impairment in UCD patients because treatment intensification is required in neonatal-onset patients with severe types of UCDs, such as neonatal-onset OTCD and CPS1D [34]. Posset et al. [35] suggested that growth impairment was determined by disease severity and associated with diminished or borderline plasma BCAA concentrations, regardless of the degree of natural protein intake. Moreover, patients with neonatal-onset UCDs exhibited severe growth impairment over time. Even patients with late-onset UCDs are likely to present growth impairment over time. However, LT could contribute to catch-up growth [35]. Unfortunately, our study did not demonstrate an association between the height and plasma BCAA levels of patients with UCDs. Plasma BCAA levels are likely to be lower in patients with CPS1D and ASLD than in patients with other UCDs; however, no significant differences were observed in this regard. Because we could only acquire information regarding plasma BCAA levels measured at a single time point during treatment, the relationship between the height and plasma BCAA levels of patients with UCDs is unclear in the present study. Future research should investigate factors related to the height of patients with UCDs.

Our research group previously reported that the mean height of male OTCD patients aged >17 years was 166.2 ± 5.5 cm, while the mean height of female OTCD patients aged >15 years was 150.3 ± 7.2 cm [19]. Therefore, our results demonstrate that the male and female adults with OTCD included in the present study were taller than those enrolled in our previous study. This may be due to the subsequent development of new medications used to treat UCDs, including sodium phenylbutyrate and citrulline.

Intellectual disorders must be considered when evaluating the long-term prognosis of patients with UCDs. Therefore, intellectual assessments are often performed in patients with UCDs. Numerous reports describe the impact of blood ammonia levels on the brain. In the present study, the intelligence level of 9 patients with neonatal-onset OTCD, 7 patients with late-onset OTCD, 5 patients with CPS1D, 4 patients with ASSD, and 2 patients with ASLD was not assessed. The actual frequency of UCD patients with impaired intelligence may be higher than that indicated in Table 2A. Moreover, visual and auditory impairments may be important clinical manifestations of UCDs, even though they occur less frequently [17,21,36].

Assessment of developmental disabilities, such as ADHD and autism, is important in patients with UCDs. Seminara et al. [23] reported that 47% (118/177) of patients enrolled in the UCD consortium in the USA presented with an intellectual disability, 38% (95/177) developed a learning disability, 20% (36/177) had ADHD, and 3% (5/177) developed autism. Therefore, the frequency of developmental disabilities in UCD patients enrolled in the present study was lower than that reported by Seminara et al. [23]. In general, little attention is paid to developmental disabilities when patients have been diagnosed with an intellectual disability. However, in UCD patients without any or with only mild intellectual impairment, clinicians should focus on and assess developmental disabilities. We therefore propose that more emphasis should be placed on the assessment of developmental disabilities and behavioral disorders in patients with UCDs in the future.

Abnormal brain MRI or CT findings were detected in 35% of patients with UCDs (Table 2). Brain disorders related to UCDs may be evidenced by neuroimaging with manifestations ranging from normal to abnormal with or without a signature appearance. In recent years, it has been demonstrated that multimodal brain MRI using T1 weighted image, T2 weighted image, T2 fluid-attenuated inversion recovery, diffusion-weighted image, functional MRI, or/and ^{1}H/^{13}C magnetic resonance spectroscopy (MRS) is effective for the identification and evaluation of pathogenic neurologic conditions in patients with UCDs [37]. In patients with OTCD, even a partial or asymptomatic OTCD, ^{1}H MRS could detect increased glutamine levels, reduced myoinositol and choline levels in the brain, including frontal and parietal white matter, frontal gray matter, posterior cingulate gray matter, and thalamus [38]. Moreover, Gyao et al. [39] reported that specific neurocognitive deficits in patients with partial OTCD were characterized by a nonverbal learning disability typically associated with white matter or subcortical dysfunction. Even if patients have average IQ scores, they manifested specific neurobehavioral phenotypes. Weaknesses were identified in nonverbal intelligence, fine motor/dexterity/speed, visual memory, attention and executive skills, and mathematics.

Diagnosis of UCD for patients with atypical or partial UCD without hyperammonemia attack, particularly diagnosis for heterozygous female OTCD, is significantly difficult. This study included a female patient with CPS1D who experienced the first hyperammonemia attack at the age of 58 years. She had experienced two childbirths more than 30 years ago. Kim et al. reported a female patient with heterozygous OTCD who was diagnosed with ADHD and received medicine such as methylphenidate and risperidone before the diagnosis of OTCD [40]. Heterozygous carriers for OTCD presented elevated plasma glutamine and alanine levels, lowered plasma citrulline levels, and increased urinary orotate excretion compared to those in non-carriers [41]. Although extensively studied, the screening for UCDs remains challenging [42,43]. Moreover, DNA analysis and enzyme assay are insufficient to

Table 2

Neurological manifestations and developmental disabilities in patients with urea cycle disorders (UCDs)[a].

A. Neurological manifestations

	Hypoglycemia	Hyperammonemia	Hyperammonemic coma	Convulsion	Impaired intelligence	Cerebral palsy	Hypertonia	Hypotonia	Muscle weakness	Skeletal muscle atrophy	Visual impairment	Auditory impairment	Abnormal brain MRI or CT	Abnormal brain waves
Neonatal-onset OTCD (N = 34)	18% (6/34)	100% (34/34)	68% (23/34)	71% (24/34)	59% (20/34)	59% (20/34)	38% (13/34)	24% (8/34)	32% (11/34)	18% (6/34)	6% (2/34)	3% (1/34)	59% (20/34)	32% (11/34)
Late-onset OTCD (N = 83)	4% (3/83)	94% (78/83)	69% (57/83)	25% (21/83)	29% (24/83)	7% (6/83)	5% (4/83)	4% (3/83)	6% (5/83)	2% (2/83)	1% (1/83)	4% (3/83)	23% (19/83)	20% (17/83)
CPS1D (N = 33)	12% (4/33)	91% (30/33)	82% (27/33)	58% (19/33)	73% (24/33)	39% (13/33)	15% (5/33)	21% (7/33)	21% (7/33)	21% (7/33)	0% (0/33)	0% (0/33)	48% (16/33)	30% (10/33)
ASSD (N = 43)	9% (4/43)	81% (35/43)	51% (22/43)	26% (11/43)	44% (19/43)	5% (2/43)	5% (2/43)	2% (1/43)	5% (2/43)	2% (1/43)	9% (4/43)	0% (0/43)	35% (15/43)	16% (7/43)
ASLD (N = 14)	0% (0/14)	93% (13/14)	71% (10/14)	64% (9/14)	86% (12/14)	14% (2/14)	0% (0/14)	21% (3/14)	29% (4/14)	0% (0/14)	14% (2/14)	0% (0/14)	21% (3/14)	57% (8/14)
ARG1D (N = 8)	13% (1/8)	100% (8/8)	25% (2/8)	50% (4/8)	50% (4/8)	63% (5/8)	25% (2/8)	0% (0/8)	25% (2/8)	38% (3/8)	13% (1/8)	13% (1/8)	38% (3/8)	38% (3/8)
Total (N = 215)	8% (18/215)	92% (198/215)	66% (141/215)	41% (88/215)	48% (103/215)	22% (48/215)	12% (26/215)	10% (22/215)	14% (31/215)	9% (19/215)	5% (10/215)	2% (5/215)	35% (76/215)	26% (56/215)

B. Developmental disabilities

	Autism	ADHD	Adjustment disorder	Learning disorder	Communication disorder	Mood disorder
Neonatal-onset OTCD (N = 34)	3% (1/34)	0% (0/34)	0% (0/34)	3% (1/34)	0% (0/34)	0% (0/34)
Late-onset OTCD (N = 83)	5% (4/83)	5% (4/83)	5% (4/83)	7% (6/83)	7% (6/83)	1% (1/83)
CPS1D (N = 33)	3% (1/33)	3% (1/33)	3% (1/33)	12% (4/33)	3% (1/33)	3% (1/33)
ASSD (N = 43)	7% (3/43)	12% (5/43)	7% (3/43)	21% (9/43)	12% (5/43)	0% (0/43)
ASLD (N = 14)	14% (2/14)	0% (0/14)	14% (2/14)	21% (3/14)	14% (2/14)	14% (2/14)
ARG1D (N = 8)	0% (0/8)	0% (0/8)	0% (0/8)	13% (1/8)	25% (2/8)	0% (0/8)
Total (N = 215)	5% (11/215)	5% (10/215)	5% (10/215)	11% (24/215)	7% (16/215)	2% (4/215)

[a] Abbreviations: OTCD, ornithine transcarbamylase deficiency; CPS1D, carbamoyl phosphate synthetase 1 deficiency; ASSD, argininosuccinate synthetase deficiency; ASLD, argininosuccinate lyase deficiency; ARG1D, arginase 1 deficiency; ADHD, attention deficit hyperactivity disorder; MRI, magnetic resonance imaging; CT, computerized tomography.

Table 3

Other clinical manifestations in patients with urea cycle disorders (UCDs)[a].

	Aversion to protein	Poor appetite	Nausea or Vomiting	Diarrhea	Elevated transaminase levels	Leukopenia	Anemia	Thrombocytopenia	Bleeding or thrombotic events
Neonatal-onset OTCD (N = 34)	6% (2/34)	24% (8/34)	47% (16/34)	0% (0/34)	56% (19/34)	9% (3/34)	29% (10/34)	15% (5/34)	9% (3/34)
Late-onset OTCD (N = 83)	23% (19/83)	24% (20/83)	51% (42/83)	2% (2/83)	45% (37/83)	5% (4/83)	7% (6/83)	7% (6/83)	8% (7/83)
CPS1D (N = 33)	0% (0/33)	15% (5/33)	36% (12/33)	6% (2/33)	48% (16/33)	9% (3/33)	30% (10/33)	21% (7/33)	6% (2/33)
ASSD (N = 43)	16% (7/43)	19% (8/43)	35% (15/43)	5% (2/43)	14% (6/43)	5% (2/43)	16% (7/43)	9% (4/43)	5% (2/43)
ASLD (N = 14)	36% (5/14)	36% (5/14)	64% (9/14)	0% (0/14)	36% (5/14)	21% (3/14)	7% (1/14)	14% (2/14)	0% (0/14)
ARG1D (N = 8)	38% (3/8)	13% (1/8)	38% (3/8)	13% (1/8)	63% (5/8)	13% (1/8)	13% (1/8)	0% (0/8)	13% (1/8)
Total (N = 215)	17% (36/215)	22% (47/215)	45% (97/215)	3% (7/215)	41% (88/215)	7% (16/215)	16% (35/215)	11% (24/215)	7% (15/215)

[a] Abbreviations: OTCD, ornithine transcarbamylase deficiency; CPS1D, carbamoyl phosphate synthetase 1 deficiency; ASSD, argininosuccinate synthetase deficiency; ASLD, argininosuccinate lyase deficiency; ARG1D, arginase 1 deficiency.

Table 4

Plasma amino acid levels in patients with urea cycle disorders (UCDs)[a].

A. Plasma amino acid levels of patients with UCDs at onset of disorder or time of diagnosis

Plasma amino acid levels (µmol/L)	Neonatal-onset OTCD (N = 28)	Late-onset OTCD (N = 65)	CPS1D (N = 24)	ASSD (N = 41)	ASLD (N = 12)	ARG1D (N = 8)	Reference (µmol/L)
Cit	3.9 (1.2–5.5)	13.9 (8.1–19.2)	ND (ND-4.3)	2120 (1075–2856)	230.7 (188.1–397.2)	30.0 (21.5–46.6)	17.1–42.6
Arg	56.1 (37.6–89.3)	47.6 (32.8–74.8)	56.7 (44.2–89.2)	181.7 (100.5–267.4)	55.4 (35.9–144.6)	527.8 (499.5–635.6)	53.6–133.6
Orn	152.0 (65.0–325.6)	52.5 (31.5–67.4)	75.5 (46.9–237.2)	62.8 (44.1–106.1)	83.2 (56.0–117.4)	48.1 (39.3–61.7)	31.3–104.7
Lys	212.4 (122.6–429.5)	191.9 (135.0–270.3)	238.9 (170.7–403.8)	162.4 (130.0–210.7)	118.9 (107.0–324.1)	104.9 (73.6–136.5)	108.7–242.2
Glu	71.1 (53.9–188.0)	64.9 (42.8–85.5)	63.0 (52.5–188.1)	57.9 (42.3–91.3)	106.1 (89.2–129.4)	46.2 (39.9–61.7)	12.6–62.5
Gln	1028.0 (762.4–3398)	936.9 (688.2–1077.4)	790.8 (509.9–2245)	579.1 (440.2–877.0)	628.3 (424.0–734.4)	614.4 (533.5–686.0)	422.1–703.8
Val	183.0 (125.7–214.8)	146.3 (117.1–196.8)	170.9 (98.2–201.1)	140.0 (99.8–177.6)	164.3 (106.1–183.9)	133.2 (115.8–144.8)	147.8–307.0
Leu	106.3 (78.5–145.6)	82.7 (58.8–112.6)	91.7 (65.5–113.4)	76.8 (57.6–104.9)	119.3 (77.9–159.4)	66.0 (54.0–77.6)	76.6–171.3
Ile	55.2 (34.5–75.3)	43.4 (33.1–57.2)	47.8 (23.7–58.1)	36.5 (23.3–51.9)	69.1 (34.3–100.2)	38.7 (30.9–50.9)	43.0–112.8
Gly	342.5 (274.7–637.7)	245.1 (185.9–330.5)	240.5 (189.1–546.5)	207.0 (175.3–228.2)	402.9 (279.6–526.3)	198.1 (152.3–242.4)	151.0–351.0
Ala	571.3 (440.2–1130)	433.3 (322.9–607.0)	450.5 (357.5–809.6)	402.3 (290.7–536.9)	376.2 (345.0–853.5)	253.9 (228.8–299.4)	208.7–522.7

B. Plasma branched chain amino acid (BCAA) levels in patients with urea cycle disorders (UCDs) receiving treatment

Plasma amino acid levels (µmol/L)	Neonatal-onset OTCD (N = 29)	Late-onset OTCD (N = 68)	CPS1D (N = 25)	ASSD (N = 41)	ASLD (N = 11)	ARG1D (N = 8)	Reference (µmol/L)
Val	147.4 (89.0–207.2)	161.6 (117.5–215.8)	114.9 (61.2–165.9)	150.0 (108.7–214.0)	124.4 (113.7–160.8)	137.5 (111.9–179.7)	147.8–307.0
Leu	73.4 (49.4–119)	79.2 (56.4–109.3)	65.0 (33.2–83.0)	70.5 (52.7–105.3)	57.8 (44.3–77.6)	61.5 (46.3–76.1)	76.6–171.3
Ile	42.8 (33.2–63.3)	43.5 (29.5–62.2)	39.6 (20.1–50.4)	36.5 (26.4–61.4)	33.2 (27.5–50.2)	42.8 (38.6–44.2)	43.0–112.8

Plasma amino acid levels are expressed as the median (interquartile range).

[a] Abbreviations: OTCD, ornithine transcarbamylase deficiency; CPS1D, carbamoyl phosphate synthetase 1 deficiency; ASSD, argininosuccinate synthetase deficiency; ASLD, argininosuccinate lyase deficiency; ARG1D, arginase 1 deficiency; Cit, citrulline; Arg, arginine; Orn, ornithine; Lys, lysine; Glu, glutamic acid; Gln, glutamine; Val, valine; Leu, leucine; Ile, isoleucine; Gly, glycine; Ala, alanine; ND, not detectable.

assess whether heterozygous carriers in OTCD develop symptoms of OTCD because of skewed X chromosomes inactivation. Elevated urinary orotic acid and orotidine concentrations after allopurinol loading test may aid the diagnosis of atypical or partial OTCD but remain challenging in terms of safety [17]. Therefore, considering family history, dietary preferences, medical history, and sex, we should carefully diagnose patients using biochemical tests and DNA analysis. Moreover, living-donor LT is performed for patients with UCDs in Japan. However, living-donor LT from heterozygous OTCD carrier donors from the patient's family is a matter of concern in the medical field [44,45]. Recipients with OTCD had developed hyperammonemia after undergoing

living-donor LT from heterozygous OTCD carrier donors. Therefore, LT from asymptomatic OTCD heterozygous donors should be avoided or performed after careful examination in the absence of a suitable donor candidate [45].

The present study evidenced that some patients with UCDs presented with complications such as bleeding or thrombosis tendency. Ihara et al. [46] reported cases of coagulopathy resulting from PIVKA-II accumulation in patients with late-onset OTCD. Moreover, Venkateswaran et al. [47] suggested that low plasma arginine levels are a possible risk for thrombosis in patients with neonatal-onset OTCD. Venous thrombosis was evidenced in a female OTCD patient who developed a

hyperammonemic crisis after childbirth [48]. Because bleeding or thrombosis events have been observed in several types of UCDs, the mechanism underlying this complication should be comprehensively investigated.

Reports regarding parturition in female patients with UCDs are available [48–52]; however, the employment and marital status of UCD patients is not well documented. The present study demonstrated that patients with late-onset UCDs were more likely to be employed and get married. Conversely, patients with neonatal-onset UCDs are likely to be intellectually impaired and have difficulty in finding employment as well as a spouse/partner. Formal social support systems in Japan provide employment support services to people with impaired intelligence. Therefore, it is expected that more UCD patients will be more involved in society in the future.

Some reports demonstrate plasma amino acid levels in different types of UCDs [5,22,29,53]. In the present study, we expected that plasma amino acid levels of patients with UCDs would be similar to those of other reports. However, plasma ornithine (Orn) and Arg levels of patients with neonatal-onset OTCD, late-onset OTCD, CPS1D, ASSD, and ASLD enrolled in the present study were higher than those reported by Kölker et al. [5]. In these UCDs, plasma Orn and Arg levels may change depending on the metabolic state of patients, even during the onset of such disorders and/or manifestations. To ensure amino acid levels can be measured and compared, blood sampling procedures need to have a certain uniformity regarding the time of retrieval, blood preservation, and the metabolic state of patients.

5. Conclusions

In the present study, we evaluated the clinical manifestations of patients with UCDs in Japan. Growth impairment is common in patients with UCDs; however, we discovered that Japanese patients with late-onset OTCD were only slightly shorter than the mean height of the general adult population in Japan. Patients with neonatal-onset UCDs may have difficulty finding employment as well as a spouse/partner; however, some patients with late-onset UCDs are employed and married. We evidenced the importance of social support in patients with UCDs presenting mild to moderate intellectual disability. In the future, the social status of patients with UCDs should be further investigated in-depth, and we advocate for social support for patients with UCDs. With the increase in social support systems in Japan, it is expected that more patients with UCDs will have the opportunity to play a more significant role in society.

Declaration of competing interest

All authors declare that there are no conflicts of interest in relation to the current study.

Author contribution

J.K and K.N were responsible for the design of the research. J.K, S.M, T.I, S.H, K.F, K.K-I, Y.M, S.Y, M.I, and N.S, contributed to practicing medicine and data collection from patients with UCDs. J.K, S.M and K.N checked and analyzed the data. J.K wrote the manuscript. J.K and K.N supervised this study. All authors read and approved the final manuscript for submission. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2021.100724.

References

[1] N. Nagata, I. Matsuda, K. Oyanagi, Estimated frequency of urea cycle enzymopathies in Japan, Am. J. Med. Genet. 39 (1991) 228–229, https://doi.org/10.1002/ajmg.1320390226.

[2] J. Kido, S. Matsumoto, H. Mitsubuchi, F. Endo, K. Nakamura, Early liver transplantation in neonatal-onset and moderate urea cycle disorders may lead to normal neurodevelopment, Metab. Brain Dis. 33 (2018) 1517–1523, https://doi.org/10.1007/s11011-018-0259-6.

[3] J.M. Saudubray, M.C. Nassogne, P. de Lonlay, G. Touati, Clinical approach to inherited metabolic disorders in neonates: an overview, Semin. Neonatol. 7 (2002) 3–15, https://doi.org/10.1053/siny.2001.0083.

[4] J. Kido, K. Nakamura, H. Mitsubuchi, T. Ohura, M. Takayanagi, M. Matsuo, M. Yoshino, Y. Shigematsu, T. Yorifuji, M. Kasahara, R. Horikawa, F. Endo, Long-term outcome and intervention of urea cycle disorders in Japan, J. Inherit. Metab. Dis. 35 (2012) 777–785, https://doi.org/10.1007/s10545-011-9427-0.

[5] S. Kölker, A. Garcia-Cazorla, V. Valayannopoulos, A.M. Lund, A.B. Burlina, J. Sykut-Cegielska, F.A. Wijburg, E.L. Teles, J. Zeman, C. Dionisi-Vici, I. Barić, D. Karall, P. Augoustides-Savvopoulou, L. Aksglaede, J.B. Arnoux, P. Avram, M. R. Baumgartner, J. Blasco-Alonso, B. Chabrol, A. Chakrapani, K. Chapman, E.C. I. Saladelafont, M.L. Couce, L. de Meirleir, D. Dobbelaere, V. Dvorakova, F. Furlan, F. Gleich, W. Gradowska, S. Grünewald, A. Jalan, J. Häberle, G. Haege, R. Lachmann, A. Laemmle, E. Langereis, P. de Lonlay, D. Martinelli, S. Matsumoto, C. Mühlhausen, H.O. de Baulny, C. Ortez, L. Peña-Quintana, D.P. Ramadža, E. Rodrigues, S. Scholl-Bürgi, E. Sokal, C. Staufner, M.L. Summar, N. Thompson, R. Vara, I.V. Pinera, J.H. Walter, M. Williams, P. Burgard, The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 1: the initial presentation, J. Inherit. Metab. Dis. 38 (2015) 1041–1057, https://doi.org/10.1007/s10545-015-9839-3.

[6] S. Kölker, V. Valayannopoulos, A.B. Burlina, J. Sykut-Cegielska, F.A. Wijburg, E. L. Teles, J. Zeman, C. Dionisi-Vici, I. Barić, D. Karall, J.B. Arnoux, P. Avram, M. R. Baumgartner, J. Blasco-Alonso, S.P. Boy, M.B. Rasmussen, P. Burgard,

B. Chabrol, A. Chakrapani, K. Chapman, E.C.I. Saladelafont, M.L. Couce, L. de Meirleir, D. Dobbelaere, F. Furlan, F. Gleich, M.J. González, W. Gradowska, S. Grünewald, T. Honzik, F. Hörster, H. Ioannou, A. Jalan, J. Häberle, G. Haege, E. Langereis, P. de Lonlay, D. Martinelli, S. Matsumoto, C. Mühlhausen, E. Murphy, H.O. de Baulny, C. Ortez, C.C. Pedrón, G. Pintos-Morell, L. Pena-Quintana, D. P. Ramadža, E. Rodrigues, S. Scholl-Bürgi, E. Sokal, M.L. Summar, N. Thompson, R. Vara, I.V. Pinera, J.H. Walter, M. Williams, A.M. Lund, A. Garcia-Cazorla, The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: the evolving clinical phenotype, J. Inherit. Metab. Dis. 38 (2015) 1059–1074, https://doi.org/10.1007/s10545-015-9840-x.

[7] S. Adam, M.F. Almeida, M. Assoun, J. Baruteau, S.M. Bernabei, S. Bigot, H. Champion, A. Daly, M. Dassy, S. Dawson, M. Dixon, K. Dokoupil, S. Dubois, C. Dunlop, S. Evans, F. Eyskens, A. Faria, E. Favre, C. Ferguson, C. Goncalves, J. Gribben, M. Heddrich-Ellerbrok, C. Jankowski, R. Janssen-Regelink, C. Jouault, C. Laguerre, S. Le Verge, R. Link, S. Lowry, K. Luyten, A. Macdonald, C. Maritz, S. McDowell, U. Meyer, A. Micciche, M. Robert, L.V. Robertson, J.C. Rocha, C. Rohde, I. Saruggia, E. Sjoqvist, J. Stafford, A. Terry, R. Thom, K. Vande Kerckhove, M. van Rijn, A. van Teeffelen-Heithoff, A. van Wegberg, K. van Wyk, C. Vasconcelos, H. Vestergaard, D. Webster, F.J. White, J. Wildgoose, H. Zweers, Dietary management of urea cycle disorders: European practice, Mol. Genet. Metab. 110 (2013) 439–445, https://doi.org/10.1016/j.ymgme.2013.09.003.

[8] S.W. Brusilow, D.L. Valle, M.L. Batshaw, New pathways of nitrogen excretion in inborn errors of urea synthesis, Lancet 314 (1979) 452–454, https://doi.org/10.1016/S0140-6736(79)91503-4.

[9] G.M. Enns, S.A. Berry, G.T. Berry, W.J. Rhead, S.W. Brusilow, A. Hamosh, Survival after treatment with phenylacetate and benzoate for urea-cycle disorders, N. Engl. J. Med. 356 (2007) 2282–2292, https://doi.org/10.1056/nejmoa066596.

[10] H. Nagasaka, T. Yorifuji, K. Murayama, M. Kubota, K. Kurokawa, T. Murakami, M. Kanazawa, T. Takatani, A. Ogawa, E. Ogawa, S. Yamamoto, M. Adachi, K. Kobayashi, M. Takayanagi, Effects of arginine treatment on nutrition, growth and urea cycle function in seven Japanese boys with late-onset ornithine transcarbamylase deficiency, Eur. J. Pediatr. 165 (2006) 618–624, https://doi.org/10.1007/s00431-006-0143-y.

[11] M.L. Batshaw, R.B. MacArthur, M. Tuchman, Alternative pathway therapy for urea cycle disorders: twenty years later, J. Pediatr. 138 (2001) S46–S55, https://doi.org/10.1067/mpd.2001.111836.

[12] K. Tanaka, K. Nakamura, S. Matsumoto, J. Kido, H. Mitsubuchi, T. Ohura, F. Endo, Citrulline for urea cycle disorders in Japan, Pediatr. Int. 59 (2017) 422–426, https://doi.org/10.1111/ped.13163.

[13] R.H. Singh, Nutritional management of patients with urea cycle disorders, J. Inherit. Metab. Dis. 30 (2007) 880–887, https://doi.org/10.1007/s10545-007-0718-4.

[14] J. Häberle, N. Boddaert, A. Burlina, A. Chakrapani, M. Dixon, M. Huemer, D. Karall, D. Martinelli, P.S. Crespo, R. Santer, A. Servais, V. Valayannopoulos, M. Lindner, V. Rubio, C. Dionisi-Vici, Suggested guidelines for the diagnosis and management of urea cycle disorders, Orphanet J. Rare Dis. 7 (2012) 32, https://doi.org/10.1186/1750-1172-7-32.

[15] S. Picca, C. Dionisi-Vici, D. Abeni, A. Pastore, C. Rizzo, M. Orzalesi, G. Sabetta, G. Rizzoni, A. Bartuli, Extracorporeal dialysis in neonatal hyperammonemia: modalities and prognostic indicators, Pediatr. Nephrol. 16 (2001) 862–867, https://doi.org/10.1007/s004670100702.

[16] S. Picca, A. Bartuli, C. Dionisi-Vici, Medical management and dialysis therapy for the infant with an inborn error of metabolism, Semin. Nephrol. 28 (2008) 477–480, https://doi.org/10.1016/j.semnephrol.2008.05.007.

[17] J. Häberle, A. Burlina, A. Chakrapani, M. Dixon, D. Karall, M. Lindner, H. Mandel, D. Martinelli, G. Pintos-Morell, R. Santer, A. Skouma, A. Servais, G. Tal, V. Rubio, M. Huemer, C. Dionisi-Vici, Suggested guidelines for the diagnosis and management of urea cycle disorders: first revision, J. Inherit. Metab. Dis. 42 (2019) 1192–1230, https://doi.org/10.1002/jimd.12100.

[18] M. Kasahara, S. Sakamoto, R. Horikawa, U. Koji, K. Mizuta, M. Shinkai, Y. Takahito, T. Taguchi, Y. Inomata, S. Uemoto, K. Tatsuo, S. Kato, Living donor liver transplantation for pediatric patients with metabolic disorders: the Japanese multicenter registry, Pediatr. Transplant. 18 (2014) 6–15, https://doi.org/10.1111/petr.12196.

[19] K. Nakamura, J. Kido, S. Matsumoto, H. Mitsubuchi, F. Endo, Clinical manifestations and growth of patients with urea cycle disorders in Japan, J. Hum. Genet. 61 (2016) 613–616, https://doi.org/10.1038/jhg.2016.17.

[20] J. Kido, S. Matsumoto, K. Momosaki, R. Sakamoto, H. Mitsubuchi, F. Endo, K. Nakamura, Liver transplantation may prevent neurodevelopmental deterioration in high-risk patients with urea cycle disorders, Pediatr. Transplant. 21 (2017), e12987, https://doi.org/10.1111/petr.12987.

[21] L. Krivitzky, T. Babikian, H.-S. Lee, N.H. Thomas, K.L. Burk-Paull, M.L. Batshaw, Intellectual, adaptive, and behavioral functioning in children with urea cycle disorders, Pediatr. Res. 66 (2009) 96–101, https://doi.org/10.1203/pdr.0b013e3181a27a16.

[22] M. Tuchman, B. Lee, U. Lichter-Konecki, M.L. Summar, M. Yudkoff, S. D. Cederbaum, D.S. Kerr, G.A. Diaz, M.R. Seashore, H.-S. Lee, R.J. McCarter, J. P. Krischer, M.L. Batshaw, Urea Cycle Disorders Consortium of the Rare Diseases Clinical Research Network, cross-sectional multicenter study of patients with urea cycle disorders in the United States, Mol. Genet. Metab. 94 (2008) 397–402, https://doi.org/10.1016/j.ymgme.2008.05.004.

[23] J. Seminara, M. Tuchman, L. Krivitzky, J. Krischer, H.-S. Lee, C. Lemons, M. Baumgartner, S. Cederbaum, G.A. Diaz, A. Feigenbaum, R.C. Gallagher, C. O. Harding, D.S. Kerr, B. Lanpher, B. Lee, U. Lichter-Konecki, S.E. McCandless, J. L. Merritt, M.L. Oster-Granite, M.R. Seashore, T. Stricker, M. Summar, S. Waisbren,

[24] M. Yudkoff, M.L. Batshaw, Establishing a consortium for the study of rare diseases: the Urea Cycle Disorders Consortium, Mol. Genet. Metab. 100 (2010) S97–S105, https://doi.org/10.1016/j.ymgme.2010.01.014.

[24] D. Jamiolkowski, S. Kölker, E.M. Glahn, I. Barić, J. Zeman, M.R. Baumgartner, C. Mühlhausen, A. Garcia-Cazorla, F. Gleich, G. Haege, P. Burgard, E-IMD consortium, Behavioural and emotional problems, intellectual impairment and health-related quality of life in patients with organic acidurias and urea cycle disorders, J. Inherit. Metab. Dis. 39 (2016) 231–241, https://doi.org/10.1007/s10545-015-9887-8.

[25] S.E. Waisbren, A.L. Gropman, Members of the Urea Cycle Disorders Consortium (UCDC), M.L. Batshaw, Improving long term outcomes in urea cycle disorders-report from the Urea Cycle Disorders Consortium, J. Inherit. Metab. Dis. 39 (2016) 573–584, https://doi.org/10.1007/s10545-016-9942-0.

[26] J.C. Fichtel, J.A. Richards, L.S. Davis, Trichorrhexis nodosa secondary to argininosuccinicaciduria, Pediatr. Dermatol. 24 (2007) 25–27, https://doi.org/10.1111/j.1525-1470.2007.00327.x.

[27] E. Trevisson, L. Salviati, M.C. Baldoin, I. Toldo, A. Casarin, S. Sacconi, L. Cesaro, G. Basso, A.B. Burlina, Argininosuccinate lyase deficiency: mutational spectrum in Italian patients and identification of a novel ASL pseudogene, Hum. Mutat. 28 (2007) 694–702, https://doi.org/10.1002/humu.20498.

[28] S. Mercimek-Mahmutoglu, D. Moeslinger, J. Häberle, K. Engel, M. Herle, M. W. Strobl, S. Scheibenreiter, A. Muehl, S. Stöckler-Ipsiroglu, Long-term outcome of patients with argininosuccinate lyase deficiency diagnosed by newborn screening in Austria, Mol. Genet. Metab. 100 (2010) 24–28, https://doi.org/10.1016/j.ymgme.2010.01.013.

[29] E. Martín-Hernández, L. Aldámiz-Echevarría, E. Castejón-Ponce, C. Pedrón-Giner, M.L. Couce, J. Serrano-Nieto, G. Pintos-Morell, A. Bélanger-Quintana, M. Martínez-Pardo, M.T. García-Silva, P. Quijada-Fraile, I. Vitoria-Miñana, J. Dalmau, R. A. Lama-More, M.A. Bueno-Delgado, M. del Toro-Riera, I. García-Jiménez, C. Sierra-Córcoles, M. Ruiz-Pons, L.J. Peña-Quintana, I. Vives-Piñera, A. Moráis, E. Balmaseda-Serrano, S. Meavilla, P. Sanjurjo-Crespo, C. Pérez-Cerdá, Urea cycle disorders in Spain: an observational, cross-sectional and multicentric study of 104 cases, Orphanet J. Rare Dis. 9 (2014) 187, https://doi.org/10.1186/s13023-014-0187-4.

[30] S.C.S. Nagamani, A. Erez, B. Lee, Argininosuccinate lyase deficiency, Genet. Med. 14 (2012) 501–507, https://doi.org/10.1038/gim.2011.1.

[31] M. Persico, M. Masarone, A. Damato, M. Ambrosio, A. Federico, V. Rosato, T. Bucci, A. Carrizzo, C. Vecchione, Non alcoholic fatty liver disease and eNOS dysfunction in humans, BMC Gastroenterol. 17 (2017) 35, https://doi.org/10.1186/s12876-017-0592-y.

[32] V.P. Tan, S. Miyamoto, Nutrient-sensing mTORC1: integration of metabolic and autophagic signals, J. Mol. Cell. Cardiol. 95 (2016) 31–41, https://doi.org/10.1016/j.yjmcc.2016.01.005.

[33] F. Molema, F. Gleich, P. Burgard, A.T. van der Ploeg, M.L. Summar, K.A. Chapman, A.M. Lund, D. Rizopoulos, S. Kölker, M. Williams, Additional individual contributors from E-IMD, Decreased plasma l-arginine levels in organic acidurias (MMA and PA) and decreased plasma branched-chain amino acid levels in urea cycle disorders as a potential cause of growth retardation: options for treatment, Mol. Genet. Metab. 126 (2019) 397–405, https://doi.org/10.1016/j.ymgme.2019.02.003.

[34] R. Posset, A.L. Gropman, S.C.S. Nagamani, L.C. Burrage, J.K. Bedoyan, D. Wong, G. T. Berry, M.R. Baumgartner, M. Yudkoff, M. Zielonka, G.F. Hoffmann, P. Burgard, A. Schulze, S.E. McCandless, A. Garcia-Cazorla, J. Seminara, S.F. Garbade, S. Kölker, Urea Cycle Disorders Consortium and the European Registry and Network for Intoxication Type Metabolic Diseases Consortia Study Group, Impact of diagnosis and therapy on cognitive function in urea cycle disorders, Ann. Neurol. 86 (2019) 116–128, https://doi.org/10.1002/ana.25492.

[35] R. Posset, S.F. Garbade, F. Gleich, A.L. Gropman, P. de Lonlay, G.F. Hoffmann, A. Garcia-Cazorla, S.C.S. Nagamani, M.R. Baumgartner, A. Schulze, D. Dobbelaere, M. Yudkoff, S. Kölker, M. Zielonka, Urea Cycle Disorders Consortium (UCDC), European registry and network for Intoxication type Metabolic Diseases (E-IMD), Long-term effects of medical management on growth and weight in individuals with urea cycle disorders, Sci. Rep. 10 (2020) 11948, https://doi.org/10.1038/s41598-020-67496-3.

[36] J.M. Anderson, M.C. Brodsky, Protracted cortical visual loss in a child with ornithine transcarbamylase deficiency, J. Neuroophthalmol. 30 (2010) 99–101, https://doi.org/10.1097/wno.0b013e3181c5d09c.

[37] K. Sen, M.T. Whitehead, A.L. Gropman, Multimodal imaging in urea cycle-related neurological disease – what can imaging after hyperammonemia teach us? Transl. Sci. Rare Dis. 5 (2020) 87–95, https://doi.org/10.3233/TRD-200048.

[38] A. Gropman, Brain imaging in urea cycle disorders, Mol. Genet. Metab. 100 (2010) S20–S30, https://doi.org/10.1016/j.ymgme.2010.01.017.

[39] K. Gyato, J. Wray, Z.J. Huang, M. Yudkoff, M.L. Batshaw, Metabolic and neuropsychological phenotype in women heterozygous for ornithine transcarbamylase deficiency, Ann. Neurol. 55 (2004) 80–86, https://doi.org/10.1002/ana.10794.

[40] S.H. Kim, J.S. Lee, B.C. Lim, K.J. Kim, Y.S. Hwang, J.D. Park, J.-E. Cheon, I.-O. Kim, B.-N. Kim, J.-H. Chae, A female carrier of ornithine carbamoyltransferase deficiency masquerading as attention deficit-hyperactivity disorder, Brain Dev. 36 (2014) 734–737, https://doi.org/10.1016/j.braindev.2013.09.009.

[41] N.E. Maestri, C. Lord, M. Glynn, A. Bale, S.W. Brusilow, The phenotype of ostensibly healthy women who are carriers for ornithine transcarbamylase deficiency, Medicine (Baltimore) 77 (1998) 389–397, https://doi.org/10.1097/00005792-199811000-00004.

[42] N. Shibata, Y. Hasegawa, K. Yamada, H. Kobayashi, J. Purevsuren, Y. Yang, V. C. Dung, N.N. Khanh, I.C. Verma, S. Bijarnia-Mahay, D.H. Lee, D.-M. Niu, G.

F. Hoffmann, Y. Shigematsu, T. Fukao, S. Fukuda, T. Taketani, S. Yamaguchi, Diversity in the incidence and spectrum of organic acidemias, fatty acid oxidation disorders, and amino acid disorders in Asian countries: selective screening vs. expanded newborn screening, Mol. Genet. Metab. Rep. 16 (2018) 5–10, https://doi.org/10.1016/j.ymgmr.2018.05.003.

[43] J.L. Merritt, L.L. Brody, G. Pino, P. Rinaldo, Newborn screening for proximal urea cycle disorders: current evidence supporting recommendations for newborn screening, Mol. Genet. Metab. 124 (2018) 109–113, https://doi.org/10.1016/j.ymgme.2018.04.006.

[44] D.A. Wong, Ornithine transcarbamylase deficiency: are carrier females suitable donors? Pediatr. Transplant. 16 (2012) 525–527, https://doi.org/10.1111/j.1399-3046.2012.01733.x.

[45] T.H. Rahayatri, H. Uchida, K. Sasaki, T. Shigeta, Y. Hirata, H. Kanazawa, V. Mali, A. Fukuda, S. Sakamoto, M. Kasahara, Hyperammonemia in ornithine transcarbamylase-deficient recipients following living donor liver transplantation from heterozygous carrier donors, Pediatr. Transplant. 21 (2017), e12848, https://doi.org/10.1111/petr.12848.

[46] K. Ihara, M. Yoshino, T. Hoshina, N. Harada, K. Kojima-Ishii, M. Makimura, Y. Hasegawa, Y. Watanabe, S. Yamaguchi, T. Hara, Coagulopathy in patients with late-onset ornithine transcarbamylase deficiency in remission state: a previously unrecognized complication, Pediatrics. 131 (2013) e327–e330, https://doi.org/10.1542/peds.2012-0030.

[47] L. Venkateswaran, F. Scaglia, V. McLin, P. Hertel, O.A. Shchelochkov, S. Karpen, D. Mahoney Jr., D.L. Yee, Ornithine transcarbamylase deficiency: a possible risk factor for thrombosis, Pediatr. Blood Cancer 53 (2009) 100–102, https://doi.org/10.1002/pbc.22016.

[48] J. Kido, T. Kawasaki, H. Mitsubuchi, H. Kamohara, T. Ohba, S. Matsumoto, F. Endo, K. Nakamura, Hyperammonemia crisis following parturition in a female patient with ornithine transcarbamylase deficiency, World J. Hepatol. 9 (2017) 343–348, https://doi.org/10.4254/wjh.v9.i6.343.

[49] S. Worthington, J. Christodoulou, B. Wilcken, B. Peat, Pregnancy and argininosuccinic aciduria, J. Inherit. Metab. Dis. 19 (1996) 621–623, https://doi.org/10.1007/bf01799836.

[50] H. Mendez-Figueroa, K. Lamance, V.R. Sutton, K. Aagaard-Tillery, I. Van den Veyver, Management of ornithine transcarbamylase deficiency in pregnancy, Am. J. Perinatol. 27 (2010) 775–784, https://doi.org/10.1055/s-0030-1254240.

[51] U. Ituk, O.C. Constantinescu, T.K. Allen, M.J. Small, A.S. Habib, Peripartum management of two parturients with ornithine transcarbamylase deficiency, Int. J. Obstet. Anesth. 21 (2012) 90–93, https://doi.org/10.1016/j.ijoa.2011.09.007.

[52] J.G. Langendonk, J.C.P. Roos, L. Angus, M. Williams, F.P.J. Karstens, J.B.C. de Klerk, C. Maritz, T. Ben-Omran, C. Williamson, R.H. Lachmann, E. Murphy, A series of pregnancies in women with inherited metabolic disease, J. Inherit. Metab. Dis. 35 (2012) 419–424, https://doi.org/10.1007/s10545-011-9389-2.

[53] S.E. Waisbren, D. Cuthbertson, P. Burgard, A. Holbert, R. McCarter, S. Cederbaum, Members of the Urea Cycle Disorders Consortium, Biochemical markers and neuropsychological functioning in distal urea cycle disorders, J. Inherit. Metab. Dis. 41 (2018) 657–667, https://doi.org/10.1007/s10545-017-0132-5.