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Clinical, biochemical, and genotypical characteristics in urea cycle mitochondrial transporter disorders

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Abstract. – BACKGROUND: This study aimed to evaluate clinical, biochemical, and genotypic findings of patients diagnosed with urea cycle mitochondrial transporter disorders.

CASE SERIES: In this study, patients followed up with the diagnosis of urea cycle mitochondrial transporter disorders in the pediatric metabolism outpatient clinic of Diyarbakir Children's Hospital were retrospectively examined. Height, weight, head circumference, gender, age at diagnosis, follow-up period, consanguinity history between parents, and treatments of the patients included in the study were evaluated. Eight patients suffering from urea cycle mitochondrial transporter disorders were enrolled in the study. Five patients were found to have biallelic variants of the *SLC25A15* gene. Two patients were found to have biallelic variants of the *SLC25A13* gene. Two of our patients presented with gait disturbances and were diagnosed with HHH syndrome. One patient presented with liver failure and was diagnosed with HHH syndrome. The other three patients were identified by family screening. Citrin deficiency was detected in two patients with cholestasis and hepatomegaly in the infantile period. Ornithine levels increased in three of our patients with HHH syndrome during the first month of treatment despite a protein-restricted diet and adequate caloric intake.

CONCLUSIONS: Increasing patients' caloric intake with HHH syndrome improves their ornithine levels. Our patients with citrin deficiency recovered clinically and biochemically before seven months.

Key Words:
Children, Family screening, Treatment, Urea cycle mitochondrial transporter disorders.

Background

The urea cycle, which converts ammonia to urea, is the primary route for eliminating waste nitrogen. Five enzymatic steps and membrane transporters that ensure the integration of the mitochondrial and cytoplasmic components of the cycle are tightly regulated for the process to function. Ornithine translocase and citrin act as membrane transporters in the urea cycle. Defects in these carrier proteins cause Hyperornithinemia-Hyperammonemia-Homocitrullinuria (HHH) syndrome and citrin deficiency, respectively.

Babies with a urea cycle mitochondrial transporter disorder appear normal at birth. HHH syndrome is a rare autosomal recessive disorder due to mutations in the *SLC25A15* gene encoding the mitochondrial ornithine transporter protein[1]. Clinical manifestations of HHH syndrome may appear in the neonatal period or later. Patients with neonatal onset present with vomiting, hypotonicity, and malnutrition[2-4]. Neurocognitive symptoms, encephalopathy, chronic liver disease, and ataxia are evident in both childhood and adult-onset forms of the disease[2,3]. Even within families, the clinical manifestations and severity of the disease vary significantly[5,6]. There is no correlation between the *SLC25A15* genotype and the clinical or biochemical phenotype of HHH syndrome. Citrin deficiency may present with intrahepatic cholestasis and growth retardation in the neonatal period and hyperammonemia in adolescence and adulthood.

HHH syndrome can be determined by DNA analysis of the *SLC25A15* gene and biochemical analysis by measuring elevated ammonia, homocitrulline, and ornithine levels. Citrin deficiency can be detected by DNA analysis of the *SLC25A13* gene and biochemical analysis by measuring high ammonia, citrulline, arginine, and threonine/serine ratio levels. Due to the history of siblings with this disease, patients can be diagnosed at birth through screening.

This study aimed to evaluate the clinical, biochemical, and genotypical findings of the patients we followed up with the diagnosis of urea cycle mitochondrial transporter disorders.

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Case Series

Study Design

This case series involved children and adolescents diagnosed with HHH syndrome and treated at our hospital between January 2022 and June 2023. Ethics committee approval was obtained from the Gazi Yaşargil Training and Research Hospital ethics committee for the study with decision number 2023/422.

Study Population

In this study, patients followed up with the diagnosis of urea cycle mitochondrial transporter disorders in the pediatric metabolism outpatient clinic of Diyarbakir Children's Hospital were retrospectively examined. The files of eight patients followed in our pediatric metabolism outpatient clinic and diagnosed with urea cycle mitochondrial transporter disorders by blood amino acids, tandem mass spectrometry, urine organic acid analysis, and molecular genetic analysis were analyzed.

Data Collection

The study evaluated the patients' height, weight, head circumference, gender, age at diagnosis, follow-up period, consanguinity history between parents, and treatments. In addition, brain MRI findings were examined. These data were obtained from the patient's electronic files in the hospital information management system. Patients whose clinical, demographic, laboratory, and neuroimaging data could not be accessed were excluded from the study.

All patients' clinical, demographic, laboratory, and imaging data were analyzed. A complete medical history was gathered from the patients or their families. Each patient underwent a physical examination at the time of the diagnosis and subsequent follow-up appointments at the metabolic clinic.

Statistical Analysis

The SPSS version 23.0 (IBM Corp., Armonk, NY, USA) statistical analysis tool was used to conduct the statistical analysis after all data had been uploaded to the computer environment. Descriptive statistics are presented with standard deviation, median, mean, minimum, maximum, frequency, and percentage values. A p-value lower than 0.05 was regarded as statistically significant.

Results

Eight patients suffering from urea cycle mitochondrial transporter disorders were enrolled in the study. In the total sample, four were male, and four were female. The median ages of the patients at the time of diagnosis were 125 (range 3-210) months. There was a history of consanguinity marriage in seven (87.5%) cases. The detailed clinical characteristics of the cases are given in Table I. The metabolic findings of the patients are shown in Table II. Five patients were found to have biallelic variants of the *SLC25A15*

Table I. Clinical and demographic characteristics of patients.

Patient No.	Gender	Age at diagnosis, years	Current age, years	Clinical symptoms	Brain MRI	Genotype	Diagnosis
1	M	16	16.8	Gait disturbance	Normal	*SLC25A15* gene homozygote c.535C>T mutation	HHH syndrome
2	F	10.4	10.9	Asymptomatic	Normal	*SLC25A15* gene homozygote c.535C>T mutation	HHH syndrome
3	M	2.33	2.8	Asymptomatic	Normal	*SLC25A15* gene homozygote c.535C>T mutation	HHH syndrome
4	M	14	14.5	Gait disturbance	Normal	*SLC25A155* gene homozygote c.535C>T mutation	HHH syndrome
5	F	17.5	17.9	Asymptomatic	Normal	*SLC25A15* gene homozygote c.535C>T mutation	HHH syndrome
6	F	5	5.4	Liver faiulure	Normal	NA	HHH syndrome
7	F	0.25	1.3	Cholestasis	NA	*SLC25A13* gene c.691G>T / c.28_29del compound heterozygous	Citrin deficiency
8	M	0.33	1.5	Cholestasis	NA	*SLC25A13* gene c.691G>T / c.28_29del compound heterozygous	Citrin deficiency

Table II. Metabolic findings of the patients.

Patient No.	Ammonium (31-123 µg/dL)	Ornithine (19-139 mmol/mol)	Homocitrullin, urine (0-140 µmol/g.creatinine)	Citrulline (4-50 mmol/mol)	Arginine (30-147 mmol/mol)	Tyrosine (24-125 mmol/mol)	Methionine (12-50 mmol/mol)	Threonine (40-428 mmol/mol)
1	73	367	782.46	28	73	56	48	90
2	61	468	423.70	26	65	32	31	75
3	83	305	1,831.21	32	48	37	39	54
4	66	446	479.01	26	43	33	27	50
5	45	436	401.07	36	44	38	29	58
6	167	248	755	26	51	72	38	54
7	55	79	NA	355	176	212	82	554
8	43	105	NA	285	210	255	144	510

gene. Two patients were found to have biallelic variants of the *SLC25A13* gene. Each parent was a heterozygous carrier for the variant found in their offspring. Patient 6 was unable to undergo genetic testing due to family issues.

Patient 1

A 16-year-old boy with normal cognitive development was referred for gait disturbance. He was the first child of consanguineous parents, and the family history did not give a clue to neurologic or inherited metabolic diseases. His previous medical history was unremarkable. His weight was 54 kg, height was 173 cm, and vital signs were stable. Physical examination was completely routine except for ataxic gait.

Laboratory analysis, including erythrocyte sedimentation rate, complete blood count, electrolytes, and renal and liver function tests, were all within normal limits. A magnetic resonance image (MRI) scan of the brain was normal. Hepatomegaly was detected in abdominal ultrasonography. A whole-exome sequencing (WES) analysis was performed on the patient, and a homozygous mutation was found in the *SLC25A15* gene. After genetic analysis, the patient was referred to our pediatric metabolism outpatient clinic, and metabolic tests were performed. Laboratory findings were as follows: blood ammonium levels 73 µg/dL (31-123 µg/dL), blood ornithine levels 367 mmol/mol (19-139 mmol/mol), urine homocitrulin levels 782.46 µmol/g creatinine (0-140 µmol/g.creatinine) (Table II). The acylcarnitine profile and urine organic acid were analyzed, and expected results were obtained. The high blood ornithine levels and high excretion of homocitrulline were compatible with the diagnosis of HHH syndrome.

The patient was put on a protein-restricted diet (0.9 g/kg/day, 2,200 kcal/day), supplemented with L-citrulline (150 mg/kg/day), L-carnitine (100 mg/kg/day) and sodium benzoate (250 mg/kg/day). Ornithine levels increased during the first month of treatment despite a protein-restricted diet and adequate caloric intake (Figure 1). Ornithine levels improved following a 10% increase in his caloric intake. The patient's condition is stable with treatment.

Patient 2

Patient 1's sister

Family screening detected a 10-year-old girl with normal cognitive development. Her previous medical history was unremarkable. Her weight was 28 kg, her height was 135 cm, and her vital signs were stable. The physical examination was regular.

Laboratory analysis, including erythrocyte sedimentation rate, complete blood count, electrolytes, blood gas, and renal and liver function tests, were all within normal limits. Other laboratory findings were as follows: blood ammonium levels 61 µg/dL (31-123 µg/dL), blood ornithine levels 468 mmol/mol (19-139 mmol/mol), urine homocitrulin levels 423.70 µmol/g. creatinine (0-140 µmol/g.creatinine) (Table II).

The acylcarnitine profile and urine organic acid were analyzed, and expected results were obtained. The brain MRI was normal. Hepatomegaly was detected in abdominal ultrasonography. The high blood ornithine levels and high excretion of homocitrulline were compatible with the diagnosis of HHH syndrome. The genetic analysis of the *SLC25A15* gene revealed homozygosity for c.535C>T mutation.

The patient was put on a protein-restricted diet (1.1 g/kg/day, 2000 kcal/day), supplemented with L-citrulline (150 mg/kg/day), L-carnitine (100 mg/kg/day) and sodium benzoate (250 mg/kg/day). Ornithine levels increased during the first month of

treatment despite a protein-restricted diet and adequate caloric intake (Figure 1). Ornithine levels improved following a 10% increase in her caloric intake. The patient's condition is stable with treatment.

Patient 3

Patient 1's brother

Family screening detected a 2-year-old boy with normal cognitive development. His previous medical history was unremarkable. His weight was 14 kg, his height was 95 cm, and his vital signs were stable. The physical examination was regular.

Laboratory analysis, including erythrocyte sedimentation rate, complete blood count, electrolytes, blood gas, and renal and liver function tests, were all within normal limits. Other laboratory findings were as follows: blood ammonium levels 83 µg/dL (31-123 µg/dL), blood ornithine levels 305 mmol/mol (19-139 mmol/mol), urine homocitrulin levels 1,831.21 µmol/g.creatinine (0-140 µmol/g.creatinine) (Table II). The acylcarnitine profile and urine organic acid were analyzed, and expected results were obtained. The brain MRI was normal. Abdominal ultrasonography was normal. The high blood ornithine levels and high excretion of homocitrulline were compatible with the diagnosis of HHH syndrome. The genetic analysis of the *SLC25A15* gene revealed homozygosity for c.535C>T mutation.

The patient was put on a protein-restricted diet (1.2 g/kg/day, 1,200 kcal/day), supplemented with L-citrulline (150 mg/kg/day), L-carnitine (100 mg/kg/day) and sodium benzoate (250 mg/kg/day). Ornithine levels increased during the first month of treatment despite a protein-restricted diet and adequate caloric intake (Figure 1). Ornithine levels improved following a 10% increase in his caloric intake. The patient's condition is stable with treatment.

Patient 4

A previously healthy 14-year-old boy had a complaint of gait disturbances 11 months before admission. His past medical history was unremarkable for trauma, genetic, or other inherited metabolic diseases. He was the second child of consanguineous parents, and the family history did not give a clue to neurologic or inherited metabolic disorders. On admission, his body temperature was 36.5°C, blood pressure 105/75 mmHg, and heart rate 85 beats/min. His weight and height were between the 10^{th}-25^{th} and 50^{th}-75^{th} percentiles, respectively. Physical examination was completely routine except for ataxic gait.

The brain MRI was normal. Laboratory analysis, including erythrocyte sedimentation rate, complete blood count, electrolytes, blood gas, and renal and liver function tests, were all within normal limits.

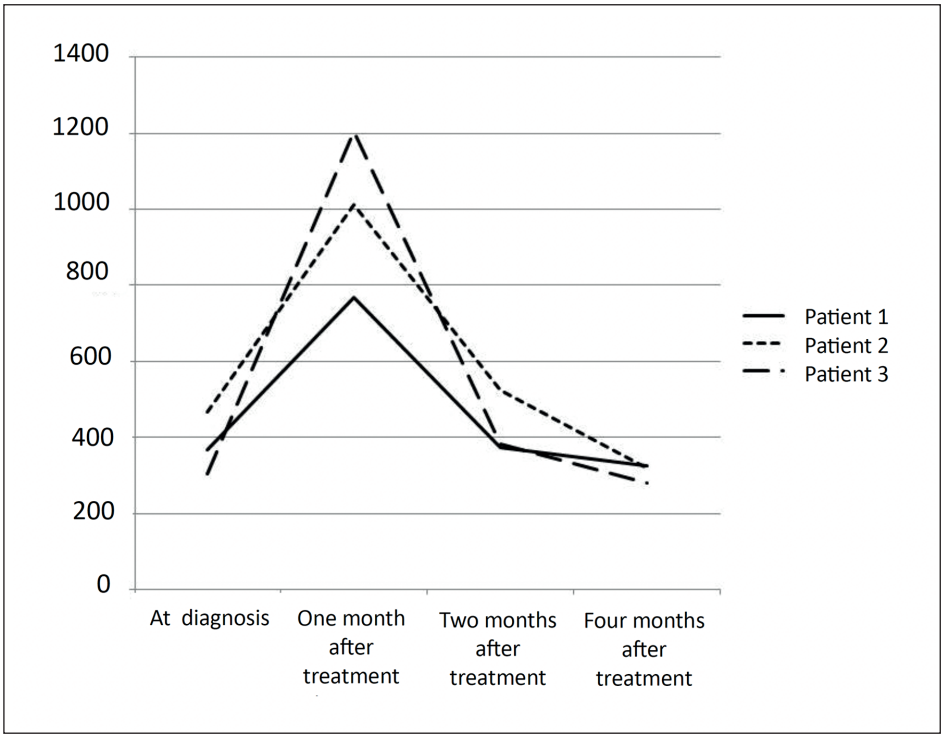

Figure 1. Ornithine levels of Patient 1, Patient 2, and Patient 3.

Other laboratory findings were as follows: blood ammonium levels 66 µg/dL (31-123 µg/dL), blood ornithine levels 446 mmol/mol (19-139 mmol/mol), urine homocitrulin levels 479.01 µmol/g.creatinine (0-140 µmol/g.creatinine) (Table II).

The acylcarnitine profile and urine organic acid were analyzed, and expected results were obtained. The high blood ornithine levels and high excretion of homocitrulline were compatible with the diagnosis of HHH syndrome. The genetic analysis of the *SLC25A15* gene revealed homozygosity for c.535C>T mutation. The patient was put on a protein-restricted diet (0.9 g/kg/day, 2,200 kcal/day), supplemented with L-citrulline (150 mg/kg/day), L-carnitine (100 mg/kg/day) and sodium benzoate (250 mg/kg/day).

Patient 5

Patient 4's sister

Family screening detected a 17-year-old girl with normal cognitive development. Her previous medical history was unremarkable. Her weight and height were between the 10^{th}-25^{th} and 50^{th}-75^{th} percentiles, respectively. The physical examination was completely routine.

Laboratory analysis, including erythrocyte sedimentation rate, complete blood count, electrolytes, blood gas, and renal and liver function tests, were all within normal limits. Other laboratory findings were as follows: blood ammonium levels 45 µg/dL (31-123 µg/dL), blood ornithine levels 436 mmol/mol (19-139 mmol/mol), urine homocitrulin levels 401.07 µmol/g.creatinine (0-140 µmol/g.creatinine) (Table II). The acylcarnitine profile and urine organic acid were analyzed, and expected results were obtained. The brain MRI and abdominal ultrasound were normal. The high blood ornithine levels and high excretion of homocitrulline were compatible with the diagnosis of HHH syndrome. Sequencing of the *SLC25A15* gene in the patient revealed a homozygote mutation c.535C>T.

The patient was put on a protein-restricted diet (0.9 g/kg/day, 2200 kcal/day), supplemented with L-citrulline (150 mg/kg/day), L-carnitine (100 mg/kg/day) and sodium benzoate (250 mg/kg/day).

Patient 6

A 5-year-old girl with normal cognitive development was referred for liver failure. She was the first child of consanguineous parents, and the family history did not give a clue to neurologic or inherited metabolic diseases. Her previous medical history was unremarkable. Her weight was 17 kg, height was 111 cm, and vital signs were stable. The physical examination was completely routine.

Laboratory analysis, including erythrocyte sedimentation rate, complete blood count, electrolytes, blood gas, and renal function tests, were all within normal limits. Other laboratory findings were as follows: SGOT levels 1,093 U/L (15-50 U/L), SGPT levels 1,795 U/L (0-45 U/L), GGT levels 36 U/L (0-30 U/L), aPTT levels 50 seconds (20-45 seconds), PT levels 31 seconds (11-16 seconds), INR 2.66 (0.9-1.4), blood ammonium levels 167 µg/dL (31-123 µg/dL), blood ornithine levels 248 mmol/mol (19-139 mmol/mol), urine homocitrulin levels 755 µmol/g.creatinine (0-140 µmol/g.creatinine) (Table II).

The acylcarnitine profile and urine organic acid were analyzed, and normal results were obtained. The brain MRI and abdominal ultrasound were normal. The high blood ornithine levels, high blood ammonium levels, and high excretion of homocitrulline were compatible with the diagnosis of HHH syndrome. Genetic testing was not performed due to family issues. The patient was put on a protein-restricted diet (1.2 g/kg/day, 1,500 kcal/day), supplemented with L-citrulline (150 mg/kg/day), L-carnitine (100 mg/kg/day), and sodium benzoate (250 mg/kg/day).

Patient 7

She was referred to the pediatric metabolism outpatient clinic because of jaundice and received the diagnosis of citrin deficiency at the age of 3 months. The pregnancy was uneventful. She was the second child of a nonconsanguineous parent. Birth weight was 3,000 gr, length was 48 cm, occipitofrontal circumference was 34 cm, and Apgar scores were 8 and 10 at 1 and 5 minutes, respectively. Her physical examination was unremarkable except for jaundice.

Laboratory investigation revealed total serum bilirubin 4.5 mg/dL (0.3-1.2 mg/dL), conjugated bilirubin 3.45 mg/dL (0-0.5 mg/dL), SGOT 125 U/L (15-60 U/L), SGPT 214 U/L (0-45 U/L). Blood glucose, lipid profile, serum electrolytes, and complete blood count were average. The acylcarnitine profile and urine organic acid were analyzed, and expected results were obtained. Other laboratory findings were as follows: blood ammonium levels 55 µg/dL (31-123 µg/dL), plasma citrulline levels: 355 mmol/mol (4-50 mmol/mol), plasma arginine 176 mmol/mol (30-147 mmol/mol), plasma methionine 82 mmol/mol (12-50 mmol/mol), plasma tyrosine 212 mmol/mol

(24-125 mmol/mol), plasma threonine 554 mmol/mol (40-428 mmol/mol), plasma threonine/serine ratio 4.07 (reference range: <1.1), blood galactose levels: 8.1 mg/dL (<10) (Table II).

The high plasma citrulline, arginine, methionine, tyrosine, threonine, threonine/serine ratio levels, cholestasis, and fatty liver were compatible with the diagnosis of citrin deficiency. Sequencing of the *SLC25A13* gene in the patient revealed a compound heterozygous mutation c.691G>T/c.28_29del. The patient has initiated fat-soluble vitamins and lactose-free formulas.

Jaundice resolved at five months of age. The amino acid profile returned to normal at six months. The patient's treatment was terminated when she was 12 months old. The patient had normal development and growth without symptoms during the 1.3-year follow-up.

Patient 8

He was referred to the pediatric metabolism outpatient clinic because of jaundice and hepatomegaly and received the diagnosis of citrin deficiency at the age of 4 months. The pregnancy was uneventful. He was the third child of consanguineous parents. Birth weight was 3,200 gr, length was 49 cm, occipitofrontal circumference was 34 cm, and Apgar scores were 9 and 10 at 1 and 5 minutes, respectively. Her physical examination was unremarkable except for jaundice and hepatomegaly.

Laboratory investigation revealed total serum bilirubin 4.8 mg/dL (0.3-1.2 mg/dL), conjugated bilirubin 3.7 mg/dL (0-0,.5 mg/dL), SGOT 145 U/L (15-60 U/L), SGPT 235 U/L (0-45 U/L). Blood glucose, lipid profile, serum electrolytes, and complete blood count were average. The acylcarnitine profile and urine organic acid were analyzed, and expected results were obtained. Other laboratory findings were as follows: blood ammonium levels 85 µg/dL (31-123 µg/dL), plasma citrulline levels 315 mmol/mol (4-50 mmol/mol), plasma arginine 185 mmol/mol (30-147 mmol/mol), plasma methionine 105 mmol/mol (12-50 mmol/mol), plasma tyrosine 315 mmol/mol (24-125 mmol/mol), plasma threonine 575 mmol/mol (40-428 mmol/mol), plasma threonine/serine ratio 3.85 (reference range: <1.1), blood galactose levels 9.5 mg/dL (<10 mg/dL) (Table II).

The high plasma citrulline, arginine, methionine, tyrosine, threonine, threonine/serine ratio levels, cholestasis, and hepatomegaly were compatible with the diagnosis of citrin deficiency. Sequencing of the *SLC25A13* gene in the patient revealed a compound heterozygous mutation c.691G>T/c.28_29del. The patient has initiated fat-soluble vitamins and lactose-free formulas.

Jaundice resolved at six months of age. The amino acid profile returned to normal at seven months. The patient's treatment was terminated when he was 12 months old. The patient had normal development and growth without symptoms during the 1.5-year follow-up.

Discussion

Eight patients suffering from urea cycle mitochondrial transporter disorders were enrolled in this study. The clinical and laboratory findings of six patients diagnosed with HHH syndrome and two patients diagnosed with citrin deficiency were evaluated. Two of our patients presented with gait disturbances and one patient presented with liver failure and was diagnosed with HHH syndrome. The other three patients were identified by family screening. Citrin deficiency was detected in two patients with cholestasis and hepatomegaly in the infantile period. Seven out of the eight patients are products of consanguineous first-cousin union. The one remaining patient's parents are not related, but they are from the same village. In our country, consanguineous marriages are prevalent[7].

The HHH syndrome has a wide range of clinical manifestations, including protein intolerance, vomiting, lethargy, liver dysfunction, and coagulopathy; in the severe form, coma and mortality may occur[4,8,9]. In addition, numerous neurological manifestations, including ataxia, mental retardation, choreoathetosis, hypotonia, peripheral neuropathy, and seizures, have been reported in association with HHH syndrome[4,8,9]. One patient presented with liver failure. Two of our patients presented with gait disturbances and were diagnosed with HHH syndrome, while the remaining three patients were identified through family screening. Patients identified by family screening were asymptomatic. Gait disturbances improved with specific dietary management and supplementation with L-citrulline, L-carnitine, and sodium benzoate.

High levels of ornithine, ammonia, and homocitrullinuria are diagnostically pathognomonic[10]. Dweikat et al[11] found elevated plasma ornithine levels in all tested patients[11]. At the initial presentation, they found that the plasma ammonia levels were increased in all patients except one patient[11]. In four cases reported by Kim et al[2], patients' blood ornithine, ammonia, and urine homocitrulline levels were all elevated[2]. However, in

our study, the ammonia level was average in all patients except one. Homocitrulline levels are analyzed at several major research facilities in our country. Therefore, if an elevated ornithine level is detected in metabolic assays, especially if clinical findings are present, the homocitrulline level should be determined first. A genetic analysis should be performed to confirm the diagnosis.

Brain MRI findings of the HHH syndrome include demyelination, abnormal white matter signal, cortical atrophy, subtentorial atrophy, stroke-like lesions, and calcifications of the basal ganglia[12-14]. The brain MRIs of our patients were found to be expected.

Treatment of the HHH syndrome includes a protein-restricted diet, citrulline supplementation, carnitine supplementation, and ammonia-scavenging medications[13,15,16]. Three patients (1, 2, and 3) had an increase in ornithine levels during the first month of treatment despite a protein-restricted diet and adequate caloric intake. Instead of restricting these three patients' protein intake, we increased their caloric intake by 10%. Ornithine levels improved after increasing their calorie intake.

Citrin deficiency is a widespread disease in Southeast Asia and the Far East but rare in Turkey. Citrin deficiency can manifest as neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD) in newborns and infants, failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD) in older children, and recurrent hyperammonemia with neuropsychiatric symptoms in citrullinemia type II (CTLN2) in adults[10,17,18]. The phenotype of our patients was determined to be NICCD. Patients 7 and 8 were diagnosed at 3 and 4 months of age, respectively. Our patients presented with jaundice and hepatomegaly. Symptoms typically resolve with treatment, including fat-soluble vitamin supplementation and lactose-free therapeutic formulations, by one year of age[18]. Our patients recovered clinically and biochemically before the age of seven months. Our patient's treatment was terminated at 12 months of age. During follow-up, our patients had normal development and growth without any symptoms.

Limitations

This study has several limitations, including its retrospective nature and small sample size. Our three patients were identified through family screening. Our patients identified by family screening were asymptomatic. Family screening is especially essential for the early diagnosis of this disease. Another limitation of our study is that only a limited number of individuals underwent family screening.

Conclusions

In conclusion, HHH syndrome should be considered in the differential diagnosis of ataxic patients. In addition, citrin deficiency should be considered in the differential diagnosis of patients with cholestasis and hepatomegaly. Despite a protein-restricted diet and adequate caloric intake, ornithine levels increased in three patients with HHH syndrome during the first month of treatment. Increasing patients' caloric information with HHH syndrome improves their ornithine levels. Even in asymptomatic patients, treatment should be initiated immediately upon diagnosis of HHH syndrome.

Informed Consent

Written informed consent was obtained from the patient's guardians.

Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

Authors' Contributions

All authors contributed to the study's conception and design. H.B., S.B., M.B., and S.T. performed material preparation, data collection, and analysis. H.B. wrote the manuscript's first draft, and all authors commented on this version. All authors read and approved the final manuscript.

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Ethics Approval

The Gazi Yaşargil Training and Research Hospital ethics committee approved the study, with decision number 2023/422.

Availability of Data and Materials

All data for this study is presented in this paper.

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