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Keywords: HHH syndrome; SLC25A15 variant; Vietnamese patients; p.Arg179*; p.Phe188del, p.Met137Cysfs*10

Article

Hyperornithinemia-Hyperammonemia-Homocitrullinuria Syndrome in Vietnamese Patients

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Abstract: Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (HHH; OMIM 238970) is one of the rarest urea cycle disorders. HHH syndrome is caused by ornithine carriers 1 deficiency which is characterized by failure of mitochondrial ornithine uptake, hyperammonemia, and accumulation of ornithine and lysine in the cytoplasm. The initial presentation and time of diagnosis in HHH is highly variable. Genetic analysis is key for diagnosis. This study included retrospective and prospective analyses of four unrelated Vietnamese children diagnosed with HHH syndrome. The age of diagnosis was from 10 days to 46 months. All four cases showed hyperornithinemia and prolonged prothrombin time. Three out of four cases presented with hyperammonemia, elevated transaminases, and uraciluria. No homocitrulline was detected in the urine. Only one case showed oroticaciduria. Genetic analyses identified three pathogenic variants in the *SLC25A15* gene. The c.535C>T (p.Arg179*) variant is a common variant in Vietnamese patients. The c.562_564del (p.Phe188del) and c.408del (p.Met137Cysfs*10) variants were found in one case. The latter variant has yet been reported in the HHH patients in the literature. After intervention with a protein-restricted diet, ammonia-reducing therapy, and L-carnitine supplementation, no case had hyperammonemia and liver enzyme levels returned to normal range. Our results highlighted clinical and biochemical heterogeneity of HHH syndrome and suggested that HHH syndrome should be considered when individuals present with hyperammonemia, elevated transaminase, and decreased prothrombine time.

Keywords: HHH syndrome; *SLC25A15* variant; Vietnamese patients; p.Arg179*; p.Phe188del; p.Met137Cysfs*10

1. Introduction

Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (HHH; OMIM 238970) is one of the rarest urea cycle disorder [1]. HHH syndrome accounts for 1-3.8% of the urea cycle disorders [2]. HHH syndrome is caused by ornithine carriers 1 deficiency which is characterized by failure of mitochondrial ornithine uptake, hyperammonemia, and accumulation of ornithine and lysine in the cytoplasm [1,3]. Homocitrulline (ε-amino-carbamoyl-lysine) is formed from carbamylation of increased cytoplasmic lysine. Patients present with protein intolerance, episodic vomiting, growth retardation, hepatomegaly, liver failure, coagulopathy, and neurological symptoms such as loss of consciousness, seizures, pyramidal signs, and cognitive impairment accompanied with or without behavioral problems [4]. Camacho summarized data from 122 patients with HHH syndrome and found the proportions of lethargy (62%), coma (33%), increased liver enzymes (52%), and coagulation disorders (49%) [5]. Long-term neurological impairments did not change with a protein-restricted diet: pyramidal tract signs (75%), intellectual disability (66%), and myoclonic epilepsy (34%). However, clinical manifestations and age of disease onset can vary widely among individuals even within the same family [5]. HHH syndrome can be diagnosed by mutations

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in the *SLC25A15* gene and elevated ammonia, homocitrulline, and ornithine levels [6]. HHH syndrome can be distinguished with other defects by high levels of urinary homocitrulline and ornithine [7]. Long-term treatment of HHH syndrome is similar to carbamoyl phosphate synthetase I and ornithine transcarbamylase deficiency [7]. Protein restriction, citrulline or arginine or essential amino acids supplementation, or sodium benzoate/sodium phenylbutyrate are required.

HHH syndrome is caused by the pathogenic variants in the *SLC25A15* gene which is an autosomal recessive pattern of inheritance [2]. The *SLC25A15* gene is located on chromosome 13q14.11 and consists of 7 exons encoding for the isoform 1 of the ornithine carrier ORC1 with a length of 301 amino acids [8]. The substrate binding of the ORC1 includes Glu77, Arg179 and Glu180 residues and the Asn74 and Asn78 are located in substrate binding pocket [9]. HHH syndrome has been more frequently reported in French-Canadian, Italian, Japanese [10], and Palestinian [11]. The major mutant alleles in the *SLC25A15* gene were p.Phe188del and p.Arg179* which are identified in 45% of HHH patients [12]. The pathogenic variants, p.Arg179*, was identified in a 5-year-old Vietnamese boy who migrated to USA [3,13]. In this study, we report the phenotype, genotype, treatment, and outcome of four Vietnamese patients diagnosed with HHH syndrome. To our best knowledge, this study is the first report of HHH patients in Vietnam.

2. Individuals and Methods

The study included retrospective and prospective analyses of four unrelated Vietnamese children diagnosed with HHH syndrome at the Center for Endocrinology, Metabolism, Genetics and Molecular Therapy, Vietnam National Hospital of Pediatrics. Case 1 is the second child of family 1 with vaginal delivery. She had normal physical and development. At 31 months of age, she presented with elevated transaminases and prolonged prothrombin time on the occasion of fever and fatigue episodes. She was diagnosed with unknown liver failure and treated with arginine and vitamin K supplement for 14 months. At 46 months of age, she showed with fatigue and lethargy she was admitted to our department. Case 2 is the second child of family 2 with vaginal delivery. After the birth, she presented poor feeding, vomiting, jaundice and lethargy was admitted to our department. Case 3 is the second child of family 3 with vaginal delivery. At 31 months of age, he exhibited fever, cough, fatigue, irritability, lethargy, hypertransaminase, and prolonged prothrombin time. He was diagnosed with liver failure and treated with glucose infusion, arginine, and vitamin K. At 48 months of age, he showed fatigue and lethargy and was admitted to our department. Case 4 is the first child of family 4, vaginal delivery. She had normal physical and development. At 18 months of age, she presented with a short convulsion (under 10 seconds) and vomiting and was admitted to our department. Biochemical investigations, such as plasma ammoniac, amino and acyl acid profiles, liver function, and coagulation were performed. The patients were managed following the previous guidelines [7]. Magnetic Resonance Imaging (MRI) was performed to identify brain abnormality.

Next generation sequencing and variant interpretation in the patients were performed at the Center for Gene-Protein Research, Hanoi Medical University. The gene panel consisted of 10 genes associated with the urea cycle disorders including *ALDH18A1*, *ARG1*, *ASL*, *ASS1*, *CPS1*, *NAGS*, *OAT*, *OTC*, *SLC25A13*, and *SLC25A15*.

3. Results

3.1. Clinical Findings

Four patients, one male and three females, were involved in this study (Table 1). There were one neonatal onset case and three late onset cases (Table 1). The age of onset was 7 days and from 18 to 31 months in the neonatal and late onset form, respectively. Cases 2 and 4 were diagnosed after a short time of onset; however, cases 1 and 3 were diagnosed 15-17 months after of onset. At the diagnosis, two cases showed poor feeding and episodic vomiting; three cases presented lethargy (Table 1). Only case 3 showed hepatosplenomegaly and case 4 showed a history of febrile seizure. Hyperammonemia, elevated transaminases, and uraciluria were observed in three/four cases (Table 1). Biochemical analyses detected hyperornithinemia and liver failure with elevated International

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Normalized Ratio (INR) but not homocitrulline in the urine in four cases. Four cases showed biochemical heterogeneity (Table 1). Case 2 showed an elevated level of ammonia but normal transaminases and uraciluria. Case 3 exhibited with a high level of transaminases (> 1000 UI/L). Oroticaciduria was only detected in case 3 (Table 1).

Table 1. Clinical features and biochemical profile of the four cases.

	Case 1	**Case 2**	**Case 3**	**Case 4**
Sexuality	Female	Female	Male	Female
Age of onset	31 months Elevated transaminases and prolonged prothrombic time	7 days Poor feeding, vomiting, jaundice, lethargy	31 months Fever, lethargy, irritability, elevated transaminases, and prolonged prothrombic time	18 months Vomiting and short convulsion
Age of diagnosis	46 months	10 days	48 months	19 months
Poor feeding	+	+	-	-
Episodic vomiting	+	+	-	-
Convulsion	-	-	-	-
Lethargy	+	+	+	-
Hepatosplenomegaly	-	-	+	-
History of fibrile seizure	-	-	-	+
Biochemical profile at the diagnosis				
Hyperammonemia (μg/dl)	+	+	+	-
	164	320	128	85
Hyperornithinemia (μmol/L)	+	+	+	+
	258.8	256.5	329.2	193.7
Elevated transaminases	+	-	+	+
✓ Alanine transaminase (UI/L)	118	30	1055	69
✓ Aspartate transaminase (UI/L)	56	19	1033	58
Prolonged Prothrombin time (%)	32	46	48	46
International normalized ratio (INR)	1.67	1.52	1.55	1.74
Uraciluria	+	-	+	+
Oroticaciduria	-	-	-	+
Homocitrullinuria	-	-	-	-

(+), present; (-) not present.

3.2. Molecular Findings

Molecular analyses of the four patients identified three variants in the *SLC25A15* gene which were classified as pathogenic variants according to ClinVar (Table 2). The variant c.535C>T (p.Arg179*) was a common variant which present in all 4 patients. Cases 1 and 2 were homozygous for the c.535C>T (p.Arg179*) variant. Case 3 harbored compound heterozygosity for c.408delC

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(p.Met137Cysfs*10) and c.535C>T (p.Arg179*). Case 4 carried compound heterozygous variants of c.535C>T (p.Arg179*) and c.562_564delTTC (p.Phe188del).

Table 2. Molecular analyses of the four cases.

Patient	Gene	Variant	dbSNP152	ClinVar
Case 1	*SLC25A15*	c.535C>T (p.Arg179*)/ c.535C>T (p.Arg179*)	rs104894429	5994 (Pathogenic)
Case 2	*SLC25A15*	c.535C>T (p.Arg179*)/ c.535C>T (p.Arg179*)	rs104894429	5994 (Pathogenic)
Case 3	*SLC25A15*	c.535C>T (p.Arg179*)/ c.408delC (p.Met137Cysfs*10)	rs104894429 rs780201405	5994 (Pathogenic) 851641 (Pathogenic)
Case 4	*SLC25A15*	c.535C>T (p.Arg179*)/ c.562_564delTTC (p.Phe188del)	rs104894429 rs202247803	5994 (Pathogenic) 5992 (Pathogenic)

Hom: homozygous; het: heterozygous.

The variant c.408delC (p.Met137Cysfs*10) has yet been reported in the HHH patients in the literature. The variant was reported by Invitae and Baylor Genetics in the ClinVar database (ID 85164) as a pathogenic or likely pathogenic variant. The variant c.408delC was observed in an East Asian at the heterozygous state (https://gnomad.broadinstitute.org/variant/13-40805209-AC-A?dataset=gnomad_r4). The variant was predicted as a deleterious variant in the Mutation Taster tool.

3.3. Treatment and Outcome

Cases 1 and 3 were misdiagnosed with unknown liver failure and treated vitamin K1 (phytok 5 mg/day) and arginine supplement, however their liver functions were not improved until they obtained accurate diagnosis. After accurate diagnosis, four cases were managed with a protein-restricted diet (1-1.5 g/kg/day), L-carnitine (100 mg/kg/day), arginine (300-500 mg/kg/day), and sodium benzoate (100-250 mg/kg/day) (Table 3). All cases responded well to the treatment with no acute hyperammonemia. Cases 1, 2, 3, and 4 were discharged after 10, 10, 7 and 5 days of treatment, respectively. After 3 days of treatment, cases 1 and 2 rapidly returned to normal levels of transaminase and coagulation. In case 4, transaminases decreased gradually to normal levels after 2 months of treatment. Meanwhile, in case 3, liver enzyme and blood clotting index improved slowly and returned to normal levels after 2 years of treatment. In the last visit, all cases showed normal level of ammoniac, normal brain magnetic resonance imaging, and normal physical development. Cases 1, 2, and 3 showed a slightly increased levels of transaminases and international normalized ratio (INR); while case 4 showed normal levels. Case 3 showed attention deficit hyperactivity disorder (Table 3). At the age of five, case 3 was diagnosed with mild deficit hyperactivity disorder and received psychotherapy intervention at home. Now, at the age of six, case 3 has improved and increased focus on learning.

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Table 3. Treatment and outcome of the four HHH cases.

	Case 1	Case 2	Case 3	Case 4
Treatment before accurate diagnosis				
Age of treament	31 months	-	31 months	-
Vitamin K1				
Arginine supplement (mg/kg/day)	300-500	-	300-500	-
Treatment after accurate diagnosis				
Age of treatment	46 months	10 days	48 months	19 months
Low protein diet (g/kg/day)				
L-carnitine supplement (mg/kg/day)	100	100	100	100
Arginine supplement (mg/kg/day)	300-500	300-500	300-500	300-500
Sodium benzoate supplement at the acute episodes (mg/kg/day)	100-250	100-250	100-250	100-250
Outcomes				
Treament time to achieve normal transaminase and coagulation	3 days	3 days	2 years	2 months
Current age	9 years	4 years	6 years	4 years
Physical development	Normal	Normal	Normal	Normal
✓ Height	- 0.6 SD	- 1.8 SD	- 0.4 SD	- 1.5 SD
✓ Weight	- 1.4 SD	-1.8 SD	- 0.4 SD	- 0.6 SD
Attention deficit hyperactivity disorder	None	None	Yes	None
Brain magnetic resonance imaging	Normal	Normal	Normal	Normal
Relapse	None	None	None	None
Biochemical profile at the last visit				
Plasma ammoniac level (μg/dl)	49	47	35	17
Transaminases				
✓ Alanine transaminase (UI/L)	34	50	47	39.3
✓ Aspartate transaminase (UI/L)	47	44	55	32.4
Prothrombin time (%)	73	75	61	81
International normalized ratio (INR)	1.25	1.22	1.43	1.15

4. Discussion

HHH syndrome is an extremely rare disorder of the urea cycle in Vietnam. Till now, only four cases have been diagnosed in our center. The diagnosis was established based on clinical, biochemical, and molecular analyses.

In our study, diverse onset age and delayed diagnosis were observed. The age of onset was from neonatal to toddler. Case 2 was presented at 10-day-old which is consistent with Camacho and colleagues pointed out that the neonatal onset rate is about 8% of people with HHH syndrome, which usually appears 24-48 hours after starting breastfeeding and the symptoms are acute [5]. Martinelli and colleagues (2015) reported that 2% of patients had symptoms in the neonatal period, 24% from 1 month to under 1 year old and 44% from 1-12 years old [2]. Although up to 1/3 of children have symptoms of neonatal onset, diagnosis is often delayed and the average diagnostic delay is 6.3 ± 10.1 years (range 0 - 37 years) [2]. In our study, case 1 and 3 were misdiagnosis of unknown liver failure, and accurate diagnosis delayed 15 months and 17 months, respectively. The causes are clinical symptoms of children with HHH syndrome are diverse and nonspecific [2,6,11]. For example, due to hyperammonemia, HHH patients showed acute neurological symptoms such as seizures, poor

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appetite, vomiting, and lethargy, which are easily misdiagnosed with encephalitis, epilepsy, cerebral hemorrhage, or poisoning. In addition, hepatosplenomegaly is also difficult to immediately suggest a metabolic disorder. Other symptoms include acute encephalopathy or chronic liver disease or cognitive impairment/learning disability/seizures.

Four cases also showed biochemical heterogeneity. Three out of them presented with hyperammonemia. The median blood ammonia concentration was usually from 100 to 300 μmol/L, in which newborns had higher average blood ammonia concentrations than older children and adults [5]. Wild et al. described a premature infant diagnosed with HHH syndrome had a blood ammonia concentration of 1,300 μmol/L when receiving intravenous nutrition and 623 μmol/L after stopping intravenous nutrition [1]. In our study, case 3 who was early onset at the age of 7 days also had the highest ammonia level (320 μg/dl). Case 4 showed a normal level of ammonia but positive oroticaciduria at the diagnosis, which were opposite to those of the other patients. Due to normal level of ammonia and elevated levels of transaminases, case 4 was mistaken for liver failure of unknown cause or autoimmune hepatitis. Therefore, we recommend that patients with unexplained liver failure should undergo repeated ammonia testing, especially when there is a change in consciousness and inborn errors of metabolism screening such as MS/MS and plasma amino acids.

In our study, four cases had hyperornithinemia, which is observed in HHH patients [2,14]. Martinelli and colleagues showed that blood ornithine concentrations of patients with HHH syndrome increased from 216-1,915 μmol/L (normal: 30–110 μmol/L) [2]. Despite treatment with medication and a protein-restricted diet, blood ornithine levels remain elevated and only a small number of patients were reported to have normal levels upon long-term follow-up [2]. Thus, the blood ornithine index is reliable in newborn screening to help with early diagnosis of HHH syndrome. No homocitrulline was detected in the urine of four cases. Homocitrullineuria is a characteristic sign of the disease, however there are patients who may have no or only very little homocitrulline excretion in the urine [11,15]. Especially in neonates, homocitrulline may be obscured by plasma amino acid profile and abnormal amino aciduria in liver dysfunction [5]. Such factors may have influenced the detection of urinary homocitrulline in our four cases.

In this study, six of eight alleles was c.535C>T (p.Arg179*), suggesting that this is a common mutation in Vietnamese patients with HHH syndrome. The c.535C>T (p.Arg179*) variant was one of the most common variants reported in a diverse HHH patients such as Japanese, Italian, Senegal, Morocco, Han Chinese, Korean, and Thailand [2]. Therefore, the c.535C>T (p.Arg179*) variant might have a wider carrier distribution in Vietnamese and could be used in population screening program. Another common variant, c.562_564delTTC (p.Phe188del), which was reported in French-Canadian [10,14,16], Italian [17], Korean [18], and Pakistan [19] also was identified in one our patient. The third variant, c.408delC (p.Met137Cysfs*10) caused a frameshift, methionine at the position amino acid 137 change to cysteine and early termination occurring at after mutation 10 amino acid.

Both cases 1 and 2 harbored the same nonsense variant c.535C>T (p.Arg179*) at the homozygous state, however they presented clinical heterogeneity. Case 2 showed neonatal onset at 7 days of age, while case 1 was late onset form at 31 months of age. In the previous study, two female patients carrying p.Arg179*/p.Arg179* variant presented symptom at neonatal period, however they showed different phenotypes [2]. It seemed to be that no correlation between the genotype and phenotype in HHH patients [11,16,19].

Before obtaining accurate diagnosis, the liver function of cases 1 and 3 had not been improved during 15 months and 17 months managed with vitamin K1 and arginine supplement. After treatment with a protein-restricted diet, L-carnitine, arginine, and sodium benzoate, liver functions of all cases had become normal. For cases 1 and 2, liver enzyme levels returned normal after 3 days of treatment, however it took 2 years and 2 months for cases 3 and 4, respectively. All cases had not occurred acute crisis of hyperammonemia during 2 – 5 years due to they were prevented by enough energy support (glucose infusion) in case of stresses (fever/vomiting/vaccination…) which is consistent with other studies . All our patients gained normal physical development. That why, more and more early accurate diagnosis for HHH syndrome is necessary, especially newborn screening.

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Diet therapy and controlling plasma ammoniac level, and preventing acute crisis from stresses allows better outcome.

No brain abnormalities were detected in brain MRI of our four cases. Neuroradiological abnormalities usually occurred after age of 20 years [20]. In our study, brain MRI were performed at the age of 4 to 9 years, therefore, neurological abnormalities have not showed in the MRI finding. In addition, after age 15, HHH patients developed spastic paraparesis which was not related to dietary intake and sodium benzoate treatment [11]. Therefore, HHH patients should be carefully long-term monitored by clinical examination, spinal and brain MRI. We suggest that MRI should be performed regularly each year after age of 15 years.

The limitations of our study include the small sample size and lack of functional test to demonstrate of the effect of pathogenic variants to protein functions *in vitro* or *in vivo*. Further studies would be needed to make a definite conclusion.

5. Conclusions

Clinical HHH syndrome is a clinical and biochemical heterogeneity disorder. Clinical spectrum is diverse and biochemical changes are nonspecific. HHH syndrome is an important factor to consider when evaluating individuals with unexplained hyperammonemia or persistently elevated liver enzymes and decreased prothrombin ratio, especially newborn screening. Pathogenic variant c. 535C>T (p.Arg179*) is common in Vietnamese cases with HHH syndrome which might be used in the screening for individuals suspected with HHH syndrome.

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