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Research paper

The phenotypic and mutational spectrum of Thai female patients with ornithine transcarbamylase deficiency

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ABSTRACT

Ornithine transcarbamylase deficiency (OTCD) is an X-linked urea cycle disorder affecting both males and females. Hemizygous males commonly present with severe hyperammonemic encephalopathy during the neonatal period. Heterozygous females have great phenotypic variability. The majority of female patients can manifest later in life or have unrecognized symptoms, making the diagnosis of OTCD in females very challenging. Here we report on three unrelated Thai female cases with OTCD presenting with different manifestations including aggressive behavior, acute liver failure and severe encephalopathy. Whole exome sequencing successfully identified disease-causing mutations in all three cases including two novel ones: the c.209_210delAA (p.Lys70Argfs*17) and the c.850T > A (p.Tyr284Asn). This study affirms variable symptoms in female patients with OTCD and emphasizes the importance of early recognition and prompt management for favorable outcomes. In addition, identification of two novel causative variants expands the genotypic spectrum of *OTC*.

1. Introduction

X-linked ornithine transcarbamylase (OTC) deficiency (OTCD, MIM #300461) accounts for approximately half of the inherited urea cycle disorders (Tuchman et al., 2008; Seminara et al., 2010; Martin-Hernandez et al., 2014; Ruegger et al., 2014). OTC is a mitochondrial enzyme which catalyzes the conversion of ornithine and carbamoyl phosphate to citrulline (Gordon, 2003). A deficiency of the enzyme leads to an impairment of the synthesis of citrulline and urea resulting in the accumulation of ammonia, glutamine, and other amino acids. The clinical presentations which are resulted from toxic effects of ammonia on the brain include altered levels of consciousness, cerebral edema or death, in severe cases. The clinical phenotypes of OTCD can generally be divided into two groups as an early onset with complete enzyme deficiency and a late onset with partial and varying enzyme activity (Brusilow and Maestri, 1996). The hemizygous males mostly present during the neonatal period and could be fatal. The heterozygous females and males with residual OTC enzyme activities can manifest with milder and later onset phenotypes. About 15%–20% of the heterozygous females are symptomatic and various clinical courses have been observed among symptomatic females (Yamaguchi et al., 2006).The neurological symptoms of OTCD vary from *sleep-wake cycle disturbances*, attention deficit, aggressive behavior, hemiparesis to coma (Kim et al., 2014). Hepatic involvement in patients with OTCD is also increasingly recognized and could lead to significant hepatocellular injury and liver failure (Gallagher et al., 2014; Laemmle et al., 2016). The clinical presentations could be precipitated by high protein intake, infection, trauma, surgery or childbirth. Due to variable clinical courses and unremarkable findings when out of crisis, the diagnosis of OTCD in females continues to be very challenging. Early recognition of clinical signs and symptoms of OTCD is essential for effective management of the condition.

The *OTC* gene which encodes ornithine transcarbamylase is located on chromosome Xp21.1 (Lindgren et al., 1984). At least 500 different

Abbreviations list: OTCD, ornithine transcarbamylase deficiency; OTC, ornithine transcarbamylase; HGMD, Human Gene Mutation Database; SIFT, sorting intolerant from tolerant; AST, aspartate transaminase; ALT, alanine transaminase; INR, international normalized ratio; MRI, magnetic resonance imaging; WES, whole exome sequencing; PCR, polymerase chain reaction; CT, computed tomography

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disease-causing variants scattered throughout the *OTC* gene have been described with the most common being missense and/or nonsense mutations (Human Gene Mutation Database (HGMD; http://www.hgmd.cf.ac.uk/ac/index.php), accessed July 2018). The splice-junction alterations, nucleotide deletions or insertions and complex rearrangements have also been reported.

Here, we report on the clinical and molecular characteristics of three unrelated heterozygous female OTCD patients with various presentations and outcomes. Three causative variants in *OTC* were identified. Two have never been previously described expanding the genotypic spectrum of *OTC*.

2. Materials and methods

2.1. Patients and families

A total of three unrelated female patients with OTCD were recruited in the study. The study was exempted by the institutional review board (IRB) of Faculty of Medicine, Chulalongkorn University, Thailand. After informed consent, blood samples from the patients and their parents were collected. The clinical manifestations and biochemical findings are summarized in Table 1.

2.2. Mutation analysis of the OTC gene

After informed consent, three milliliters of peripheral blood were taken from the patients and their available parents. Genomic DNA was extracted from peripheral blood leukocytes by using a Puregene blood kit (Qiagen, Hilden, Germany). The DNA samples were sent to Macrogen Inc., Seoul, Korea for whole exome sequencing. The sequencing libraries were enriched by SureSelect Human All Exon V5 kits. The captured libraries were sequenced using Illumina HiSeq 2000 Sequencer. Sequence reads were mapped against UCSC hg19 using Burrows-Wheeler Alignment (BWA) software (http://bio-bwa.sourceforge.net/). The single-nucleotide polymorphisms (SNPs) and Indels were detected by SAMTOOLS (http://samtools.source forge.net/) and annotated by dbSNP&1000G. Trio-WES analysis was performed and all SNVs and Indels were filtered to include splicing and exonic variants. For the missense variants, the potential pathogenicity was analyzed using SIFT (Sorting Intolerant From Tolerant; http://sift.bii.a-star.edu.sg/www/SIFT_seq_submit2.html) and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/). In addition, the variants were subsequently filtered out if they were present in our in-house database of 1084 unrelated Thai exomes. The variants would be called novel if they were not listed in the ClinVarMiner database (https://clinvarminer.genetics.utah.edu/) and the Exome Aggregation Consortium database (exac.broadinstitute.org/). The identified variants were verified by PCR-Sanger sequencing. The primer pair E2F&R 5′ CTGGGCCACAGAGTGA GAAC 3′ and 5′ TCCCTCTTTCTTTGGGAAGG 3′ was used for detection of the c.209_210delAA (p.Lys70fs*17). In addition, the c.850T > A (p.Tyr284Asn) was detected by using the primer pair E8F&R 5′ TGCC TTTTACTGTCCCATGA 3′ and 5′ AGCACAAAAATGCCTTTCCA 3′. Amino acid conservation was analyzed using Ensembl Orthologue alignment (https://doi.org/10.1093/database/bav096).

3. Results

3.1. Clinical and biochemical findings

Patient 1 was a 2-year and 10-month old girl who was a product of non-consanguineous parents. Her perinatal period was uneventful. There was no family history of seizure, intellectual impairment, metabolic disorder or sudden death. She had delayed speech with her first word at age 2 years. Increasing hyperactivity, sleep-wake disturbances as well as sudden episodes of aggression and self-mutilation were noted at the age of 2 years and 6 months. No food preference was reported. The patient was referred to our hospital due to worsening of aggressive behavior and protracted vomiting. Upon hospitalization, physical examination revealed bruises on her forehead, left eyelid and left leg, an abrasion on her left hand and intention tremors. Other examinations were unremarkable. Laboratory investigations revealed elevated ammonia levels (344 μmol/L; reference range 17–70 μmol/L) with transaminitis (total bilirubin 0.86 mg/dL, direct bilirubin 0.34 mg/dL, aspartate transaminase (AST) 1267 IU/L, alanine transaminase (ALT) 1629 IU/L, ALP 264 IU/L, albumin 4.1 g/dL, total protein 7 g/dL). The International Normalized Ratio (INR) was 1.43. Plasma L-glutamine was 315.4 μmol/L (reference range: 71.9–429.8 μmol/L), alanine was 303.2 μmol/L (reference range: 98.6–341.9 μmol/L), and citrulline was 66.8 μmol/L (reference range: 0–40.5 μmol/L) (Table 1). Urine organic acid analysis performed 2 days after cessation of enteral feeding showed nonspecific findings. Other laboratory findings including complete blood count, blood gas, electrolytes, autoimmune antibodies, viral

Table 1
Clinical and molecular characteristics of Thai female patients with OTCD.

	Patient 1	Patient 2	Patient 3
Age at diagnosis	2 years and 10 months	4 years	5 years
Development	Delay	Appropriate	Delay
Presenting symptom	Aggressive behavior	Sleep-wake disturbance and hallucination	Severe encephalopathy
Initial serum ammonia (μmol/L)	344	153	1926
AST (IU/L)	1267	1668	273
ALT (IU/L)	1629	2660	249
Glutamine[a]	315.4	N/A	483.9
(μmol/L)	(range, 71.9–429.8)		(range, 129.0–589.3)
Glutamic acid[a]	330.7	N/A	69.14
(μmol/L)	(range, 25.4–433.9)		(range, 49.4–214.4)
Citrulline[a]	66.8	N/A	60.4
(μmol/L)	(range, 0–40.5)		(range, 10.7–154.9)
Neuroimaging study	Increased signal intensity in periventricular and deep white matter of bilateral cerebral hemispheres	Normal	Diffused brain edema
Nucleotide change	c.209_210delAA	c. 482A > G	c. 850T > A
(read depths of the reference/	(15, 8)	(22/19)	(63/51)
alternate alleles)	Novel	Known	Novel
Amino acid change	p.Lys70Argfs*17	p.Asn161Ser	p.Tyr284Asn
Maternal status	Non-carrier	N/A	Carrier

N/A, not available.
[a] Different reference range according to age groups and laboratory data.

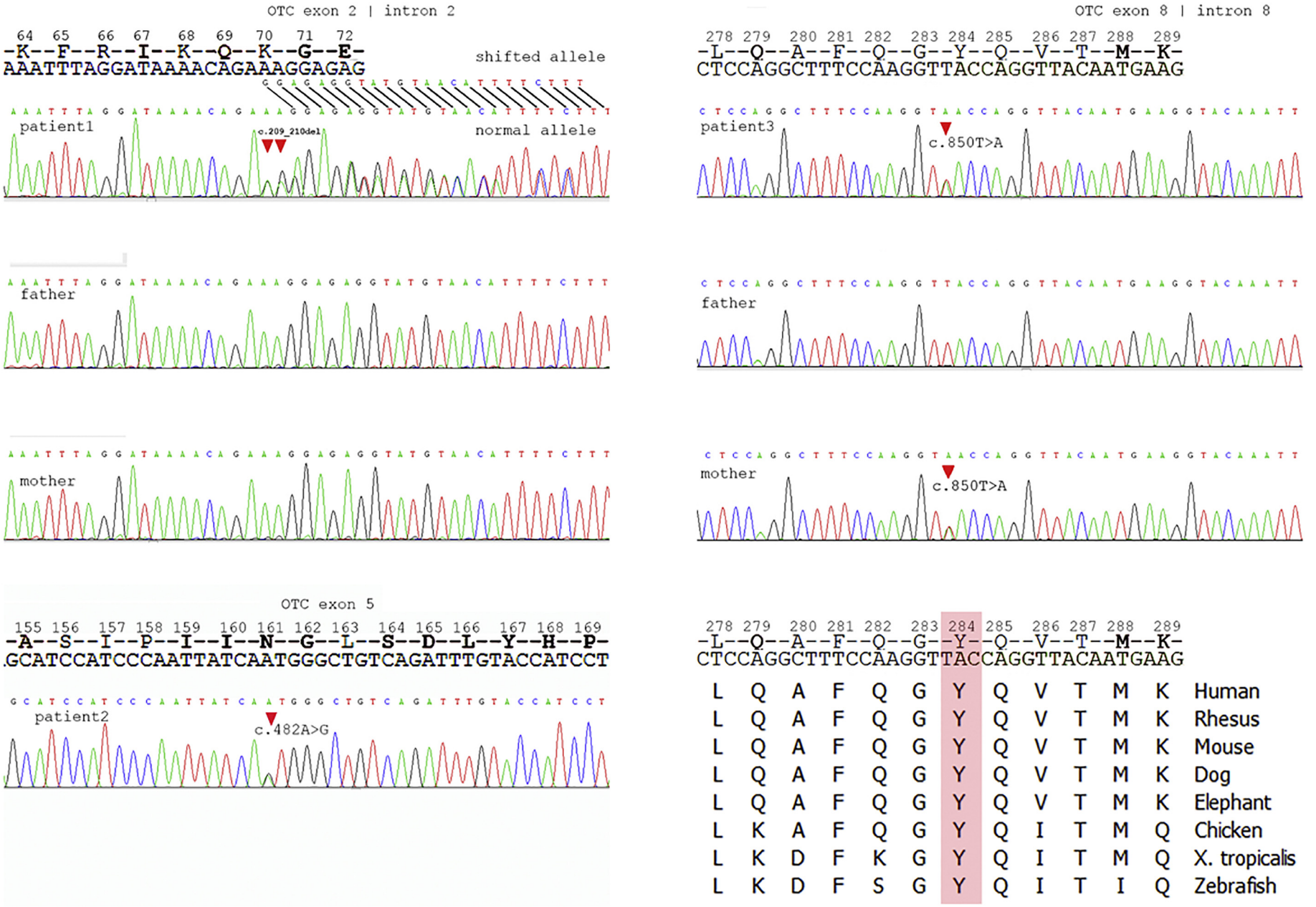

Fig. 1. Mutation analysis of the *OTC* gene. (A) Electropherograms showing the c.209_210delAA (p.Lys70Argfs*17) (upper left), the c. 482A > G (p.Asn161Ser) (lower left) and the c.850T > A (p.Tyr284Asn) (upper right) mutations. The site of each mutation is indicated by an arrow head. (B) Sequence alignment of partial amino acid sequence of OTC from various species. The tyrosine residue at codon 284 is indicated by a gray bar.

hepatitis profile, cerebrospinal fluid examination and culture studies were unremarkable. Magnetic resonance imaging (MRI) of the brain revealed bilateral symmetrical increased signal intensity in periventricular areas and deep white matter of bilateral cerebral hemispheres. Electroencephalography demonstrated sharp waves at bilateral temporal regions.

Based on clinical findings of hyperammonemic encephalopathy, urea cycle defect was suspected. Whole exome sequencing (WES) revealed a novel heterozygous frameshift mutation in the *OTC* gene (c.209_210delAA, p.Lys70Argfs*17). PCR-Sanger sequencing confirmed the presence of this mutation in the patient. However, it was absent in the mother (Fig. 1). Treatments included protein restriction, sodium benzoate and L-arginine. Fluctuations in mental status and aggressive behavior improved. After discharge, she never experienced any metabolic decompensation. At the last follow-up visit when the patient was 7 years old, she developed comprehensible speech and had entered kindergarten.

Patient 2 was a 4-year-old girl who was referred to our hospital for evaluation of the causes of acute liver failure. The patient was the second child of non-consanguineous parents. Her elder sister passed away at 1 year of age due to unspecified congenital heart disease. She was in good health until 6 weeks prior to admission, when she developed abdominal pain, nausea, vomiting, and drowsiness. Initial investigations revealed serum AST and ALT of 176 IU/L and 1450 IU/L, respectively, total bilirubin of 0.3 mg/dL, alkaline phosphatase of 746 IU/L, albumin of 3.5 g/dL, and INR of 4.4. The workup for other causes of liver disease, including viral hepatitis, Wilson disease, and autoimmune antibodies, was negative.

Upon referral to our hospital, she developed *visual hallucinations and sleep-wake cycle disturbances. Physical examination revealed alert and oriented, no jaundice*, and no hepatosplenomegaly. An ankle clonus, extensor plantar response, and hyperreflexia were not observed. Laboratory investigations showed *persistently elevated transaminases and INR.* Additional investigations revealed an elevated ammonia level of 153 μmol/L with unremarkable urine organic acid and plasma amino acid analyses. Computed tomography (CT) of the head demonstrated no abnormalities. After correction of coagulopathy, a percutaneous liver biopsy was performed. Histology revealed mild steatosis.

These findings raised a strong suspicion of a urea cycle disorder. WES was therefore performed. A known heterozygous missense variant c. 482A > G (p.Asn161Ser) in the *OTC* gene was identified. The presence of this causative variant was verified by PCR-Sanger sequencing. The parental samples were unavailable. Sodium benzoate, arginine, and lactulose were initiated. The patient was placed on a low-protein diet (< 1 g/kg daily). At her 30-month follow-up visit, she was doing well with appropriate growth and development as well as normal liver function.

Patient 3 was a 5-year-old girl presenting with severe encephalopathy after influenza A infection. She was the first child of non-consanguineous parents. Her perinatal period was uneventful. Six months prior to admission, she had one episode of unexplained encephalopathy in which the parents reported incontinence, screaming and episodes of “blanking out”. The symptoms gradually resolved within a week during admission at the local hospital. Brain MRI revealed multiple small scattered hypersignal intensity lesions at bilateral subcortical white matter. Electroencephalogram done at 10 days after the episode was normal. Family history revealed no similar findings in other members. The parents reported her speech to be more delayed than her 3-year-old sister. She attended an age appropriate class with no developmental regression. The patient was referred to our hospital after another episode of severe encephalopathy following a febrile illness with influenza A infection. Two days after the onset of fever, she became agitated and was unable to communicate verbally. Upon arrival to the intensive care unit, the patient was stuporous and her condition declined rapidly. Within < 24 h, she became comatose. Her pupils were dilated and showed no response to light. Diffused brain edema was noted on a brain CT scan. Laboratory investigations showed Hb of 11.1 g/dL, Hct 33.4%, WBC 6370/mm^3, platelets 408,000/mm^3, total bilirubin 0.59 mg/dL, direct bilirubin 0.34 mg/dL, AST 273 IU/L, ALT 249 IU/L, ALP 183 IU/L, albumin 3.8 g/dL and total protein 7.5 g/dL. Plasma ammonia level of 1926 μmol/L was noted. Biochemical studies obtained after the patient was on intravenous fluid for 48 h demonstrated normal levels of plasma L-glutamine, glutamic acid, and citrulline (Table 1). Urine orotate was detected qualitatively on urine organic acid analysis. Despite prompt administration of continuous renal replacement therapy and full resuscitative measures, the patient did not survive.

WES revealed a novel heterozygous missense c.850T > A (p.Tyr284Asn) variant in the *OTC* gene. Using PCR-Sanger sequencing, this variant was also present in her mother (Fig. 1).

4. Discussion

In this study, we reported three unrelated female OTCD patients with variable presenting symptoms including neurologic disturbances and acute liver failure. Patients 1 and 3 were noted to have developmental delay prior to the development of acute decompensation. Patient 3 had one previous episode of unexplained encephalopathy. We successfully identified the disease associated variants in all cases. Of the three different variants, two have never been previously described. Two novel alterations, the c.209_210delAA (p.Lys70Argfs*17) and the c.850T > A (p.Tyr284Asn) were found in patients 1 and 3, respectively. The previously known c. 482A > G (p.Asn161Ser) was identified in patient 2 (Tuchman and Plante, 1995).

Plasma concentrations of glutamine and alanine which serve as storage forms of waste nitrogen, are frequently elevated in urea cycle defects (Brusilow and Maestri, 1996). Low plasma citrulline concentration and elevated urine orotic acid are typically observed in symptomatic heterozygous females with OTCD (Choi et al., 2015). However, Tummolo A. et al. reported a 13-year-old female with OTCD with normal biochemical parameters and normal levels of urinary orotic acid during acute mental confusion. This discrepancy between clinical and biochemical findings has been described and suggested to be resulted from the effect of low protein intake during acute decompensation (Burlina et al., 2006; Tummolo et al., 2013). Rajabi F. et al. also reported a 13-month-old female with OTCD presented with irritability, right arm weakness and liver dysfunction with normal plasma amino acid profile and no elevation of urinary orotate performed four days after an initial presentation (Rajabi et al., 2018). In three cases reported here, plasma amino acid analysis revealed nonspecific findings during acute illnesses and urine orotate was detectable only in case 3. The mechanisms explaining atypical biochemical findings in these patients remain elusive. Therefore, mutation analysis is necessary for diagnostic confirmation.

The incidence of acute liver failure found in patient 2 is not well-defined in OTCD. It has been previously considered as an uncommon presentation (Rajabi et al., 2018). Cumulative evidence has suggested that acute liver failure is a surprisingly common complication of OTCD. Laemmle et al. reported acute liver failure in all 9 males and 6 of 20 (30%) females with OTCD (Laemmle et al., 2016). A Chinese single center study reported elevated INR (INR > 1.5) in 6/17 (35%) of males with OTCD and up to 5/7 (71%) symptomatic female counterparts (Shao et al., 2017). A historical cohort study on 71 patients with OTCD reported acute liver failure (defined by acute liver injury with an INR ≥ 2.0) about 58% in neonatal males and 56% among females with severe disease (defined by symptomatic hyperammonemia after two days of life, requirement of maximal medical and dietary therapy, and frequent hospitalizations) (Gallagher et al., 2014). Hepatic transaminase enzymes might be normal in some OTCD cases despite extreme hyperammonemia and impaired liver synthetic function assessed by elevated INR values (Laemmle et al., 2016; Shao et al., 2017). The findings of elevated serum ammonia levels in combination with irreversibly prolonged INR despite vitamin K administration should alert

the physicians to the possible diagnosis of OTCD regardless of serum transaminase levels.

As observed in patient 3, hyperammonemic encephalopathy could result in coma and lead to death in OTCD patients. Data from a European *multicenter retrospective* study revealed 43% mortality rate in patients with neonatal onset OTCD which was the highest compared with those affected with other urea cycle disorders (Unsinn et al., 2016). Previous studies have reported the survival rate of symptomatic female OTCD patients being 80–90% with favorable prognosis (Summar et al., 2008; Brassier et al., 2015; Choi et al., 2015). However, it could be lower if the symptomatic females encountered frequent hyperammonemia episodes, extremely elevated ammonia levels, serous hepatic dysfunction, and recurrent infection (Shao et al., 2017). Early recognition together with prompt and effective treatment could therefore prevent fatal outcomes.

Two novel alterations, the c.209_210delAA (p.Lys70Argfs*17) and the c.850 T > A (p.Tyr284Asn) were found in patients 1 and 3, respectively. The c.209_210delAA is an out of frame deletion affecting the aspartate/ornithine carbamoyltransferase, carbamoyl-P binding domain and is expected to result in a shortened protein from 354 to 85 amino acids long. This truncated protein product had lost the binding and active sites which could abolish either enzymatic activity or folding of OTC. The newly identified c.850T > A (p.Tyr284Asn) in patient 3 was inherited from her mother. Several lines of evidence suggest this variant as a disease-causing mutation. It was not identified in the 1084 in-house exomes. The tyrosine residue at codon 284 is located in the aspartate/ornithine carbamoyltransferase, Asp/Orn binding domain and highly conserved (Fig. 1). PolyPhen-2 predicted the c.850T > A (p.Tyr284Asn) to be probably damaging with a score of 1.000. In addition, SIFT predicted it to be damaging with a score of 0.000.

In conclusion, the diagnosis of OTCD should be considered in patients with unexplained behavioral, hepatic or neurological disorders associated with hyperammonemia at any age. There is a high phenotypic variability in heterozygous females. As a result, delayed diagnosis of OTCD in heterozygous females is often encountered. The prompt recognition of this disorder and timely commencement of appropriate therapy are essential to prevent irreversible neurological sequelae and avoid unfavorable consequences.

Conflict of interest

The authors have no conflicts of interest to disclose.

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References

Brassier, A., Gobin, S., Arnoux, J.B., Valayannopoulos, V., Habarou, F., Kossorotoff, M., Servais, A., Barbier, V., Dubois, S., Touati, G., Barouki, R., Lesage, F., Dupic, L., Bonnefont, J.P., Ottolenghi, C., De Lonlay, P., 2015. Long-term outcomes in ornithine transcarbamylase deficiency: a series of 90 patients. Orphanet J. Rare Dis. 10, 58.

Brusilow, S.W., Maestri, N.E., 1996. Urea cycle disorders: diagnosis, pathophysiology, and therapy. Adv. Pediatr. Infect. Dis. 43, 127–170.

Burlina, A.B., Peduto, A., Di Palma, A., Bellizzi, A., Sperli, D., Morrone, A., Burlina, A.P., 2006. An unusual clinical and biochemical presentation of ornithine transcarbamylase deficiency in a male patient. J. Inherit. Metab. Dis. 29, 179–181.

Choi, J.H., Lee, B.H., Kim, J.H., Kim, G.H., Kim, Y.M., Cho, J., Cheon, C.K., Ko, J.M., Lee, J.H., Yoo, H.W., 2015. Clinical outcomes and the mutation spectrum of the OTC gene in patients with ornithine transcarbamylase deficiency. J. Hum. Genet. 60, 501–507.

Gallagher, R.C., Lam, C., Wong, D., Cederbaum, S., Sokol, R.J., 2014. Significant hepatic involvement in patients with ornithine transcarbamylase deficiency. J. Pediatr. 164, 720–725 e6.

Gordon, N., 2003. Ornithine transcarbamylase deficiency: a urea cycle defect. Eur. J. Paediatr. Neurol. 7, 115–121.

Kim, S.H., Lee, J.S., Lim, B.C., Kim, K.J., Hwang, Y.S., Park, J.D., Cheon, J.E., Kim, I.O., Kim, B.N., Chae, J.H., 2014. A female carrier of ornithine carbamoyltransferase deficiency masquerading as attention deficit-hyperactivity disorder. Brain and Development 36, 734–737.

Laemmle, A., Gallagher, R.C., Keogh, A., Stricker, T., Gautschi, M., Nuoffer, J.M., Baumgartner, M.R., Haberle, J., 2016. Frequency and pathophysiology of acute liver failure in Ornithine Transcarbamylase Deficiency (OTCD). PLoS One 11, e0153358.

Lindgren, V., de Martinville, B., Horwich, A.L., Rosenberg, L.E., Francke, U., 1984. Human ornithine transcarbamylase locus mapped to band Xp21.1 near the Duchenne muscular dystrophy locus. Science 226, 698–700.

Martin-Hernandez, E., Aldamiz-Echevarria, L., Castejon-Ponce, E., Pedron-Giner, C., Couce, M.L., Serrano-Nieto, J., Pintos-Morell, G., Belanger-Quintana, A., Martinez-Pardo, M., Garcia-Silva, M.T., Quijada-Fraile, P., Vitoria-Minana, I., Dalmau, J., Lama-More, R.A., Bueno-Delgado, M.A., Del Toro-Riera, M., Garcia-Jimenez, I., Sierra-Corcoles, C., Ruiz-Pons, M., Pena-Quintana, L.J., Vives-Pinera, I., Morais, A., Balmaseda-Serrano, E., Meavilla, S., Sanjurjo-Crespo, P., Perez-Cerda, C., 2014. Urea cycle disorders in Spain: an observational, cross-sectional and multicentric study of 104 cases. Orphanet J. Rare Dis. 9, 187.

Rajabi, F., Rodan, L.H., Jonas, M.M., Soul, J.S., Ullrich, N.J., Wessel, A., Waisbren, S.E., Tan, W.H., Berry, G.T., 2018. Liver failure as the presentation of ornithine transcarbamylase deficiency in a 13-month-old female. JIMD Rep. 40, 17–22.

Ruegger, C.M., Lindner, M., Ballhausen, D., Baumgartner, M.R., Beblo, S., Das, A., Gautschi, M., Glahn, E.M., Grunert, S.C., Hennermann, J., Hochuli, M., Huemer, M., Karall, D., Kolker, S., Lachmann, R.H., Lotz-Havla, A., Moslinger, D., Nuoffer, J.M., Plecko, B., Rutsch, F., Santer, R., Spiekerkoetter, U., Staufner, C., Stricker, T., Wijburg, F.A., Williams, M., Burgard, P., Haberle, J., 2014. Cross-sectional observational study of 208 patients with non-classical urea cycle disorders. J. Inherit. Metab. Dis. 37, 21–30.

Seminara, J., Tuchman, M., Krivitzky, L., Krischer, J., Lee, H.S., Lemons, C., Baumgartner, M., Cederbaum, S., Diaz, G.A., Feigenbaum, A., Gallagher, R.C., Harding, C.O., Kerr, D.S., Lanpher, B., Lee, B., Lichter-Konecki, U., McCandless, S.E., Merritt, J.L., Oster-Granite, M.L., Seashore, M.R., Stricker, T., Summar, M., Waisbren, S., Yudkoff, M., Batshaw, M.L., 2010. Establishing a consortium for the study of rare diseases: the Urea Cycle Disorders Consortium. Mol. Genet. Metab. 100 (Suppl. 1), S97–105.

Shao, Y., Jiang, M., Lin, Y., Mei, H., Zhang, W., Cai, Y., Su, X., Hu, H., Li, X., Liu, L., 2017. Clinical and mutation analysis of 24 Chinese patients with ornithine transcarbamylase deficiency. Clin. Genet. 92, 318–322.

Summar, M.L., Dobbelaere, D., Brusilow, S., Lee, B., 2008. Diagnosis, symptoms, frequency and mortality of 260 patients with urea cycle disorders from a 21-year, multicentre study of acute hyperammonaemic episodes. Acta Paediatr. 97, 1420–1425.

Tuchman, M., Lee, B., Lichter-Konecki, U., Summar, M.L., Yudkoff, M., Cederbaum, S.D., Kerr, D.S., Diaz, G.A., Seashore, M.R., Lee, H.S., McCarter, R.J., Krischer, J.P., Batshaw, M.L., Urea Cycle Disorders Consortium of the Rare Diseases Clinical Research, N, 2008. Cross-sectional multicenter study of patients with urea cycle disorders in the United States. Mol. Genet. Metab. 94, 397–402.

Tuchman, M., Plante, R.J., 1995. Mutations and polymorphisms in the human ornithine transcarbamylase gene: mutation update addendum. Hum. Mutat. 5, 293–295.

Tummolo, A., Favia, V., Bellantuono, R., Bellino, V., Ranieri, A., Morrone, A., De Palo, T., Papadia, F., 2013. Successful early management of a female patient with a metabolic stroke due to ornithine transcarbamylase deficiency. Pediatr. Emerg. Care 29, 656–658.

Unsinn, C., Das, A., Valayannopoulos, V., Thimm, E., Beblo, S., Burlina, A., Konstantopoulou, V., Mayorandan, S., de Lonlay, P., Rennecke, J., Derbinski, J., Hoffmann, G.F., Haberle, J., 2016. Clinical course of 63 patients with neonatal onset urea cycle disorders in the years 2001–2013. Orphanet J. Rare Dis. 11, 116.

Yamaguchi, S., Brailey, L.L., Morizono, H., Bale, A.E., Tuchman, M., 2006. Mutations and polymorphisms in the human ornithine transcarbamylase (OTC) gene. Hum. Mutat. 27, 626–632.