Clinical Case Report

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Clinical and cranial MRI features of female patients with ornithine transcarbamylase deficiency

Two case reports

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Abstract

Introduction: Ornithine transcarbamylase deficiency (OTCD) is a common metabolic disease of urea circulation disorder. We reported the clinical, brain imaging and genetic characteristics of 2 cases with OTCD. The patients' clinical features, novel gene mutations, cranial MR specific imaging changes and blood tandem mass spectrometry, and urine gas chromatography-mass spectrometry were, retrospectively, analyzed.

Patient concerns: Patient 1 was a 1.6-year-old female. She was admitted to the hospital with 2-months history of general irritability and disturbance of consciousness for a day. Patient 2 was a 3.7-year-old female. She was admitted to the hospital due to decline of language ability and irritability for 5 days. Blood tandem mass spectrometry and urine gas chromatography-mass spectrometry showed uracil and orotate increased significantly in urine while amino acids in the urea cycle ring were in the normal range. The features of brain MRI are consistent with those of urea circulatory disorders. Gene detection showed 1 novel mutation in the OTC gene (c.658C>T) in patient 1 and, 1 novel mutation (c.298+2T>G) in the OTC gene in patient 2.

Diagnosis: Combined with metabolic screening and gene detection, both patients were diagnosed with OTCD.

Interventions: The patients' condition improved after following a low protein diet and receiving treatments for decreasing blood ammonia, energy supplement, correcting acid-base imbalance, and other symptomatic treatments.

Outcomes: After prompt symptomatic treatment, the consciousness and cognition of the children improved. Besides, liver function also improved significantly.

Conclusions: For patients with neurological symptoms and unexplained increase in transaminase and ammonia, OTCD should be considered as a possible diagnosis. Brain MRI can help the diagnosis of genetic metabolic encephalopathy and reflect the level of brain injury. Metabolic screening and genetic detection are helpful to make a confirmed diagnosis.

Abbreviations: ALT = Alanine aminotransferase, APTT = Activated partial thromboplastin time, AST = Aspartate aminotransferase, DWI = Diffusion weighted imaging, FSE = Fast spin echo, HGMD = the Human Gene Mutation Database, MRI = magnetic resonance imaging, OTCD = Ornithine transcarbamylase deficiency, PT = Prothrombin time, SE = Spin echo, T1WI = T1-weighted imaging, T2-FLAIR = 'T2-fluid-attenuated inversion recovery, T2WI = T2-weighted imaging, VEEG = Video electroencephalogram.

Keywords: female, magnetic resonance, ornithine transferase deficiency, OTC gene

Editor: N/A.

This work was supported by grants from the Science & Technology Department of Sichuan Province (No. 2018SZ0123)

This study was approved by the Ethics Committee of the West China Second University Hospital.

Informed written consent was obtained from the patient's parents for publication of this case report and accompanying images.

The authors have no conflicts of interests to disclose.

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Medicine (2019) 98:33(e16827)

Received: 26 December 2018 / Received in final form: 9 June 2019 / Accepted: 23 July 2019

http://dx.doi.org/10.1097/MD.0000000000016827

1. Introduction

Ornithine transcarbamylase deficiency (OTCD) is a common metabolic disease of urea circulation disorder. The disease is characterized by high blood ammonia and abnormal liver function, which often lead to the damage of the nervous system and liver function.[1,2] After common causes, such as infection and liver diseases leading to an increase in ammonia and aminotransferase had been excluded, we need to be alert about this disease. Early symptomatic treatment should be provided to avoid serious neurological injury.

OTCD is an X-linked genetic disorder involving a mutation of the ornithine transcarbamylase gene. Most males present early symptoms in the neonatal period with more devastating outcomes which often attract attention. There is a high phenotypic variability in heterozygous females.[3] In some researches, most females exhibited normal development without neurological sequelae.[4] Female patients with severe clinical manifestations are considered relatively rare. When compared to currently existing literature, we found that female patients do still present with very obvious symptoms

Here, we report the clinical, biochemical, brain image, and molecular findings of 2 female patients with OTCD who presented with outstanding symptoms. Thus, female patients can also have serious clinical manifestations, without prompt treatment, it may lead to severe neurological damage.

2. Methods

2.1. MRI test

A 1.5T MRI equipment of Philips Achieva with Nova Dual HP was used in our cases. Scanning parameters: head coil, Spin echo (SE) sequence, T1WI axial and saggital position, TR 488ms, TE 15ms, slice thickness 6 mm, recon voxel size 0.6 mm, matrix 244×164, FOV was AP 220 mm, RL 184 mm, FH 125 mm; Fast spin echo (FSE) T2WI, axial position, TR 4000ms, TE 100ms, flip angle 90, slice thickness 6 mm, recon voxel size 0.449 mm, matrix was 292×179, FOV was AP 220 mm, RL 184 mm, FH 125 mm; T2-fluid-attenuated inversion recovery sequence (T2 Flair), axial position, TR/TI 6800/2000ms, TE 120ms, slice thickness 6 mm, gap 1 mm, matrix was 236×138; DWI, axial position, b value was 1000 second/mm^2 and a baseline image with a b value of 0 second/mm^2.

2.2. Gene detection

For exome sequencing, we fragmented 1 to 3 μg of genomic DNA, extracted from each sample, to an average size of 180 bp with a Bioruptor sonicator (Diagenode). Paired-end sequencing libraries then were prepared using a DNA sample prep reagent set 1 (NEBNext). Library preparation included end repair, adapter ligation and PCR enrichment, and was carried out as recommended by Illumina protocols. The amplified DNA was captured use GenCap Deafness capture kit. The DNA probes were designed to tile along the exon regions of the OTC gene. The capture experiment was conducted according to manufacturer's protocol.

3. Case report

3.1. Patient 1 information and laboratory data

Patient 1 was a 1.6-year-old female. She was admitted to the hospital with 2-months history of general irritability and disturbance of consciousness for a day. The family denied history of aspirin intake and exposure to poisonous substances during the course of the disease. The patient was born at term. Antenatal history and the neonatal period were unremarkable. Her mother suffered from 2 miscarriages which had no apparent cause. The patient's brother died 3 days after birth. The cause was unknown. Up to the date of the current study, she had normal developmental milestones and growth parameters. When the patient was admitted to hospital, she was in light coma and no yellow staining was found in the skin and sclera. Bilateral pupils were equal round with normal light response. Neck rigidity was absent (-). The liver was located 3 cm below the rib with no tenderness. The muscle tension of the extremities was low and the pathological reflex was negative. The blood routine is unremarkable with no abnormalities. Liver function: ALT 869U/L (reference:0–40IU/L), AST337U/L (reference: 0–40IU/L), Serum bilirubin was normal. PT 42.3S (reference: 9.4–15.4S), APTT 67.1S (20.6–40.6S), blood ammonia level was 214 μmol/L (reference: 9–30 μmol/L), Pyruvic acid 135.9 μmol/L (reference: 20–100 μmol/L). Investigations for liver disease, drug and infections were all negative. Hepatitis markers, EB virus and Torch were negative. Serum ceruloplasmin was normal. The examination of cerebrospinal fluid was normal. There was no obvious abnormality in ultrasonography of abdominal and extrahepatic bile ducts. The Video electroencephalogram (VEEG) was normal. Blood tandem mass spectrometry and urine gas chromatography-mass spectrometry showed uracil and orotate increased significantly in urine while amino acids in the urea cycle ring were in the normal range.

3.1.1. Brain MRI. In patient 1 with 2 months history of general irritability, extensive abnormal signals were showed in bilateral cerebral cortex, basal ganglia and thalami (Fig. 1).

3.1.2. Detection of pathogenic genes. c.658C>T mutation which is identified in patient 1 is a missense mutation which leads to an amino acid change from Pro to Ser (p.Pro220Ser). This mutation does not belong to polymorphic sites and occurs at a very low frequency in the population. In addition, this variation has not been reported in the HGMD Professional Edition database. Analysis of pedigree verification: the father of the patient has no variation at the point while the mother has a heterozygous mutation at the point. (Fig. 2)

3.1.3. Treatment. The liver enzyme ALT increased to 2146U/L and AST increased to 2067U/L during the treatment of patient 1. She received plasma exchange twice. Besides, the patient was restricted to protein intake after the metabolic screening reports were returned. Hyperammonemia rapidly reduced following intravenous administration of glucose liquid, arginine and L-carnitine. Also, we tried to correct electrolyte disorder and maintain acid-base balance. After prompt symptomatic treatment, the consciousness and cognition of the child improved. Liver function improved significantly.

3.2. Patient2 information and laboratory data

Patient 2 was a 3.7-year-old female. She was admitted to the hospital due to decline of language ability and irritability for 5 days. She was the only child of her parents. Family members denied the history of any special hereditary diseases. When she was admitted in the hospital, she was irritable and could not respond appropriately. No yellow staining was found in the skin and sclera. Bilateral pupils were equal round with normal light

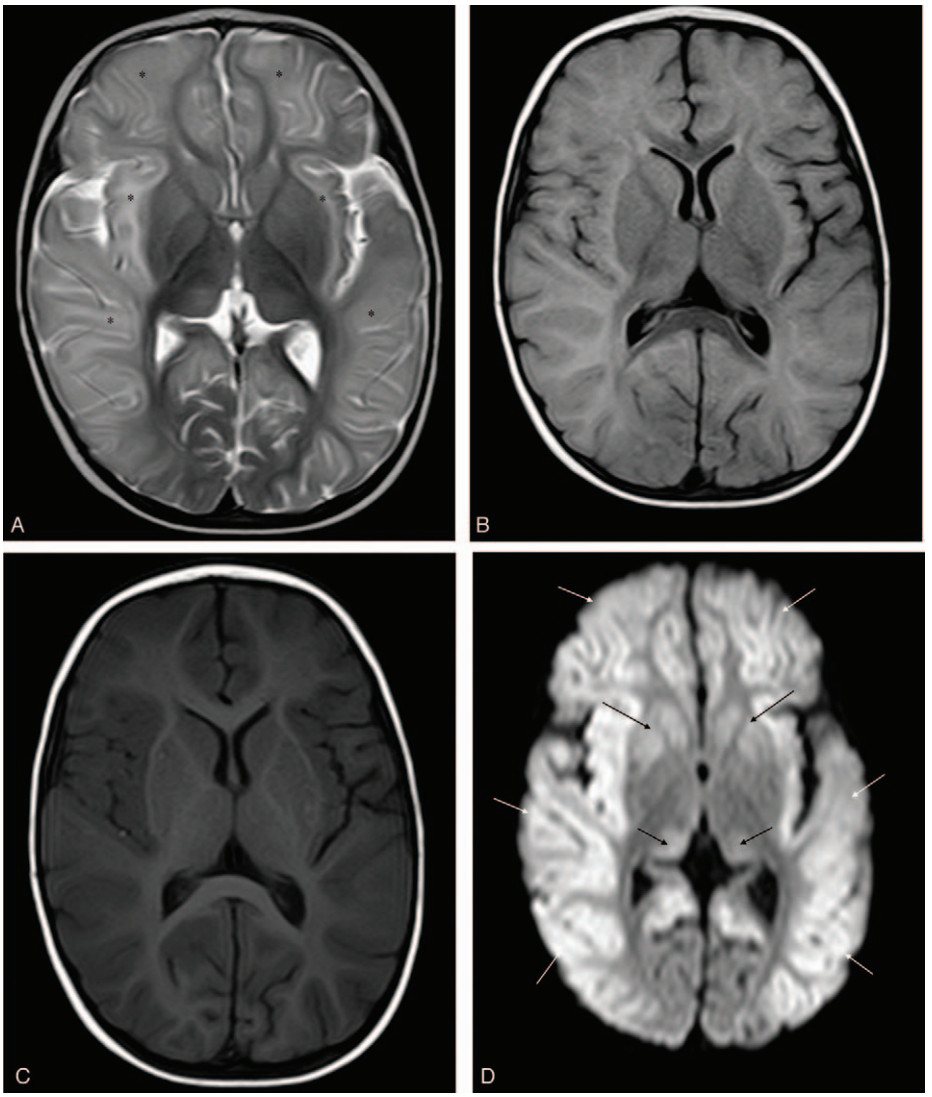

Figure 1. Brain MR images of the patient 1 with 2 months history of general irritability. T2-weighted cranial magnetic resonance image (A) and T2-weighted Flair image (B) at the level of the basal ganglia demonstrated extensive symmetrically increased signal (*) in the frontal, insular, temporal, parietal, and occipital cortices. T1-weighted image (C) showed symmetrically decreased signal in bilateral cerebral cortex. Diffusion-weighted image (D) showed symmetrically restricted diffusion in bilateral cerebral cortex involving all lobes diffusely (white arrow). The basal ganglia (short black arrow) and thalami (long black arrow) also had obvious involvement.

reflection. Neck resistance and the pathological reflex were negative. The liver and spleen were not palpable. The blood routine was unremarkable. Liver function: ALT437U/L (reference: 0–40IU/L), AST178U/L (reference: 0–40IU/L). Serum bilirubin was normal. The blood coagulation function was normal. Blood ammonia level was94umol/L (reference: 9–30 μmol/L). Investigations for liver disease, drugs and infections were all negative. The examination of cerebrospinal fluid was normal and the antibodies of autoimmune encephalitis were negative. There was no obvious abnormality in ultrasonography of the abdomen. The VEEG showed sharp and slow waves which appeared many times. Blood tandem mass spectrometry and urine gas chromatography-mass spectrometry showed increase of C18-OH, reduction of threonine and valine, while uracil and orotate were increased significantly in urine. The urine gas chromatography-mass spectrometry of patient's mother also showed slight increase of uracil and orotate while the patient's father's examination was normal.

3.2.1. Brain MRI. In patient 2, diffuse and symmetrical swelling in the bilateral frontal and insular cortices and restricted diffusion were obvious (Fig. 3). After 15 days treatment, all the abnormal signal disappeared (Fig. 4).

3.2.2. Detection of pathogenic genes. c.298+2T>G mutation in the patient 2 occurs at positions 298+2 of the nucleotide sequence. The mutation was identified as a heterozygous mutation which leads to a splicing mutation in the amino acid. This mutation does not belong to polymorphic sites and occurs to a very low frequency in the population. And this variation has not been reported in the HGMD Professional Edition database.

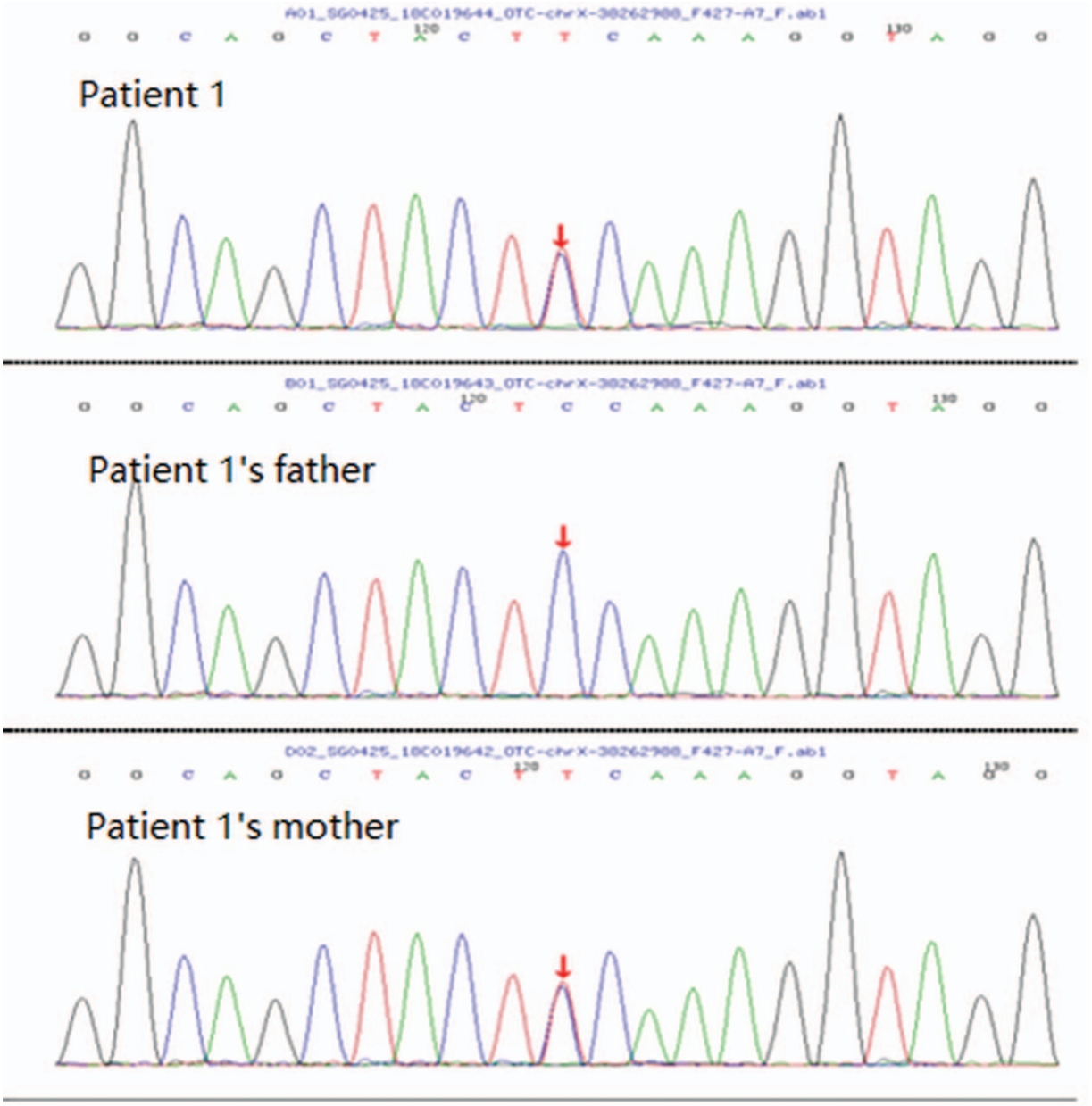

Figure 2. Patient 1's pedigree analysis.

Analysis of pedigree verification: the father of the patient has no variation in the point while the mother has a heterozygous mutation at the point. (Fig. 5)

3.2.3. Treatment. The patient was treated with protein restriction with a special formula, arginine, and L-carnitine. After the patients were discharged, a low protein diet was continued. They had follow-ups in nutrition and neurology clinic.

4. Discussion

OTC gene is a pathogenic gene of OTCD which is an X linked genetic disease. The symptoms may occur at any age. Severe vomiting, anorexia, lethargy, convulsions, coma, and even death may occur during the neonatal stage. Some infants have a variety of clinical manifestations which may be associated with elevated levels of protein intake or fasting, trauma, surgery, infection, and other increased catabolism.[5] Early clinical manifestations of hyperammonemia are nonspecific and often lead to a delay in the diagnosis of OTCD. Neurological symptoms include convulsions, behavioral abnormalities, irritability, cognitive decline, and unexplained hyperammonemic coma.[6–9] Hyperammonemia after parturition in a female patient with OTCD can be fatal. Therefore, it is important to perform an early intervention before hyperammonemia occurs in patients with OTCD or in carriers after parturition.[10]

Data showed that 2/3OTCD patients are caused by heredity; the others are caused by new mutations. Most of

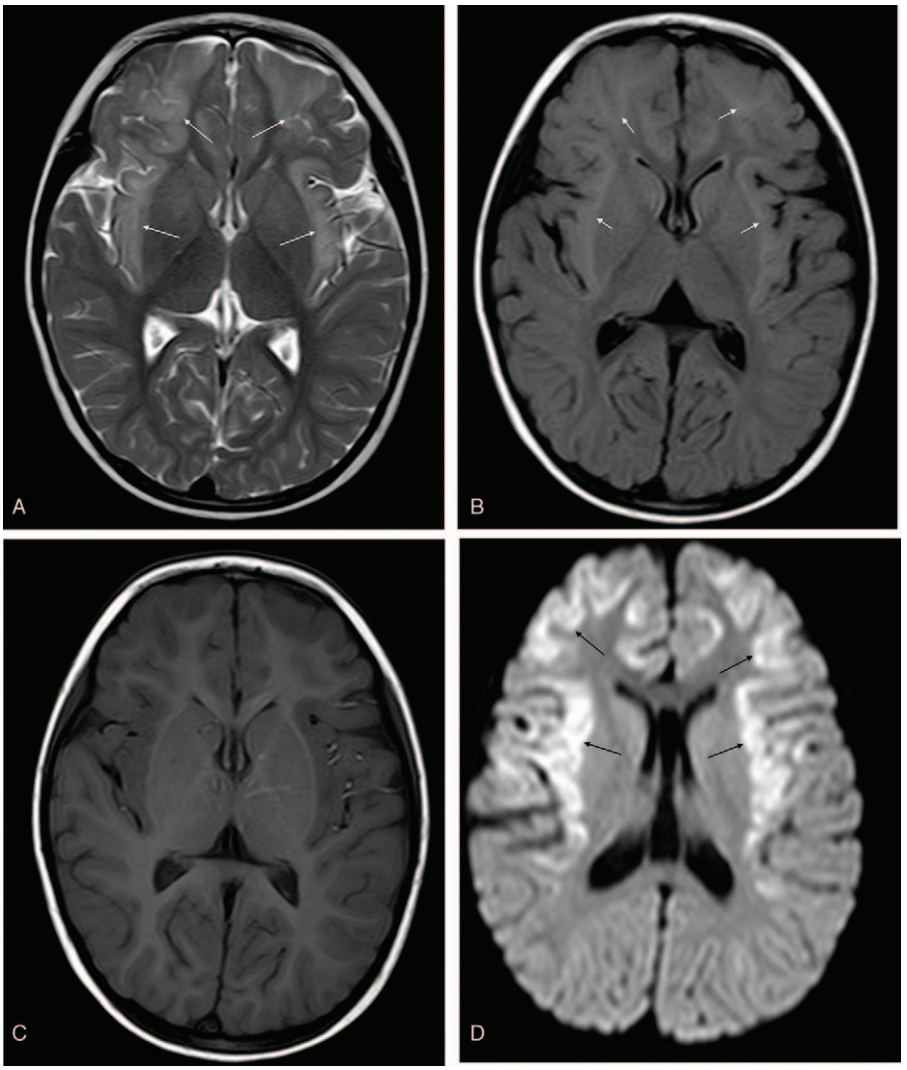

Figure 3. MR images in patient 2 before the treatment. T2WI (A) and FLAIR (B) image demonstrated symmetrical hyperintense lesions and swelling in the bilateral frontal and insular cortices (white arrow). T1-weighted image (C) showed symmetrical decreased signal in bilateral frontal and insular cortex. DWI (D) showed symmetrical restricted diffusion in the frontal and insular cortices (black arrow).

the mutations (approximately 84%) causing OTC deficiency consist of single-base substitutions, while smaller proportions consist of small deletions or insertions (12%) and larger deletions (4%).[11] There is a significant correlation between the variation type and phenotype of the gene. In the 2006 update, 341 mutations were reported. This current update contains 417 disease-causing mutations.[12] In our study, gene detection showed one novel mutation in the OTC gene (c.658C>T) in patient 1 and, 1 novel mutation (c.298+2T>G) in the OTC gene in patient 2. Clinical manifestations varied between patients, further study will be required to understand the functional changes in the proteins due to different mutations of OTC gene.

Most of the male patients suffer from the lack of activity of OTC enzymes in the liver cells, often have early onset and are dangerous. However, some non-random inactivation female carriers may not have abnormal performance; male patients are therefore more likely to receive attention. If the patient had clinical manifestations such as abnormal psychiatric behavior, cognitive decline, recurrent seizures, and disturbance of consciousness while cranial magnetic resonance also indicates abnormality, it may be misdiagnosed as other diseases such as viral encephalitis, autoimmune encephalitis or mental illness. It is necessary to check the cerebrospinal fluid, virus antibody, autoimmune antibody, electroencephalogram, and other related examination. Urine metabolic screening and genetic examination are helpful for definitive diagnosis.[13] According to the research of Takanashi J,[14] the injury of the lentiform nuclei and insular regions might be caused by hypoperfusion secondary to hyperammonemia and hyperglutaminemia. The degree of brain injury varied according to the age of onset of the patient and the duration of hyperammonia. Brain MRI can reflect the extent of brain injury of those patients. Gropman A's research found that white matter tracts underlying specific pathways involved in working memory and executive function are altered in

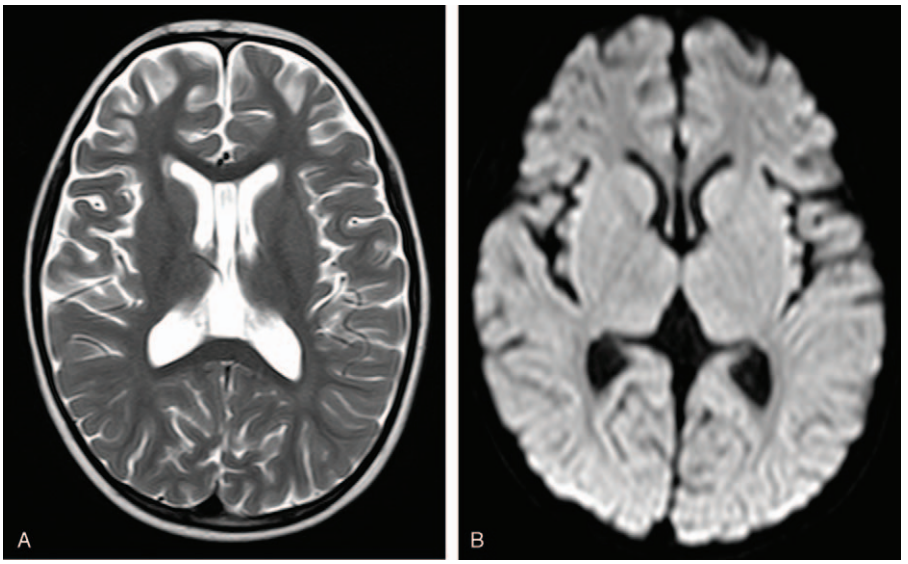

Figure 4. MR images in patient 2 obtained 15 days treatment after the onset of symptoms. T2WI image (A) demonstratedabnormal signal disappeared and symmetrical atrophyin the bilateral frontal and insular cortices. DWI (B) image showed no restricted diffusion.

subjects with OTCD (as measured by DTI), including those heterozygous women who were previously considered asymptomatic.[15] Patient 1 with earlier onset age, higher levels of ammonia and longer duration had severe clinical symptoms. In addition to insular and peri insular brain tissue damage, bilateral temporal lobe, parietal lobe, occipital lobe, basal ganglia, and dorsal thalamus also showed extensive and symmetrical damage. Patient 2 had delayed age of onset, milder degree of hyper ammonia, and shorter duration. Her brain MRI showed that the extent of brain injury was limited. The lesions were symmetrical which involved bilateral insular, peri-insular and frontal cortex and subcortical white matter. MRI may show normal or mild limitation of the range of brain injury in patients with mild and short duration of hyperammonemia. But extensive brain damage may be seen in patients with moderate to severe and prolonged hyperammonemia. Combined with the literature and our cases, the cerebral parenchyma around bilateral insular lobes and cerebral lobes were the first areas affected in patients with OCTD, then bilateral frontal lobes, parietal lobes and temporal lobes were further injured, and finally bilateral occipital lobes were injured. Occipital lobe brain damage can affect vision and even cause cortical blindness. The MR findings presumably showed the distribution of brain injury, and our MR imaging findings were similar with those reports with OTCD in the neonatal period.[14] So MRI examination can help us to discover the severity of brain damage and changes with treatment.

Both of these patients in this paper were female. They had an increase in aminotransferase previously, but they had been considered as other diseases which caused abnormal liver function. Until neurological symptoms appeared and the other common causes were excluded, the patients had been considered as this disease and received blood tandem mass spectrometry and urine gas chromatography-mass spectrometry test. But the patients had obvious nervous system damage. The mother of the first patient had a history of unexplained miscarriages and a son died within days of birth. We should be alert about inherited metabolic diseases. Therefore, doctors should be aware of OTCD when patients have gastrointestinal symptoms, abnormal liver function, increased serum ammonia and symptoms of encephalopathy. Brain MRI can help the diagnosis of genetic metabolic encephalopathy and reflect the level of brain injury. Metabolic screening and genetic detection are helpful to make a confirmed diagnosis. In addition, the prenatal gene diagnosis is practicable to determine whether the next child is OCTD gene carrier, which is of great significance in reducing birth defects during the mother's second pregnancy. Early diagnosis may prevent severe neurological complications and improve the prognosis. Liver transplantation is believed to reduce blood ammonia levels and improving the quality of life of patients. However, some studies suggest that the improvement in cognition after liver transplantation may not occur shortly. Impairment of intelligence quotient (IQ), attention and behavior disorders persists after surgery, and long-term follow-up observation is needed in these children.[16] Gene therapy may be a promising treatment in the future.

Acknowledgments

The authors thank the patient's parents for providing permission to use the information of their children.

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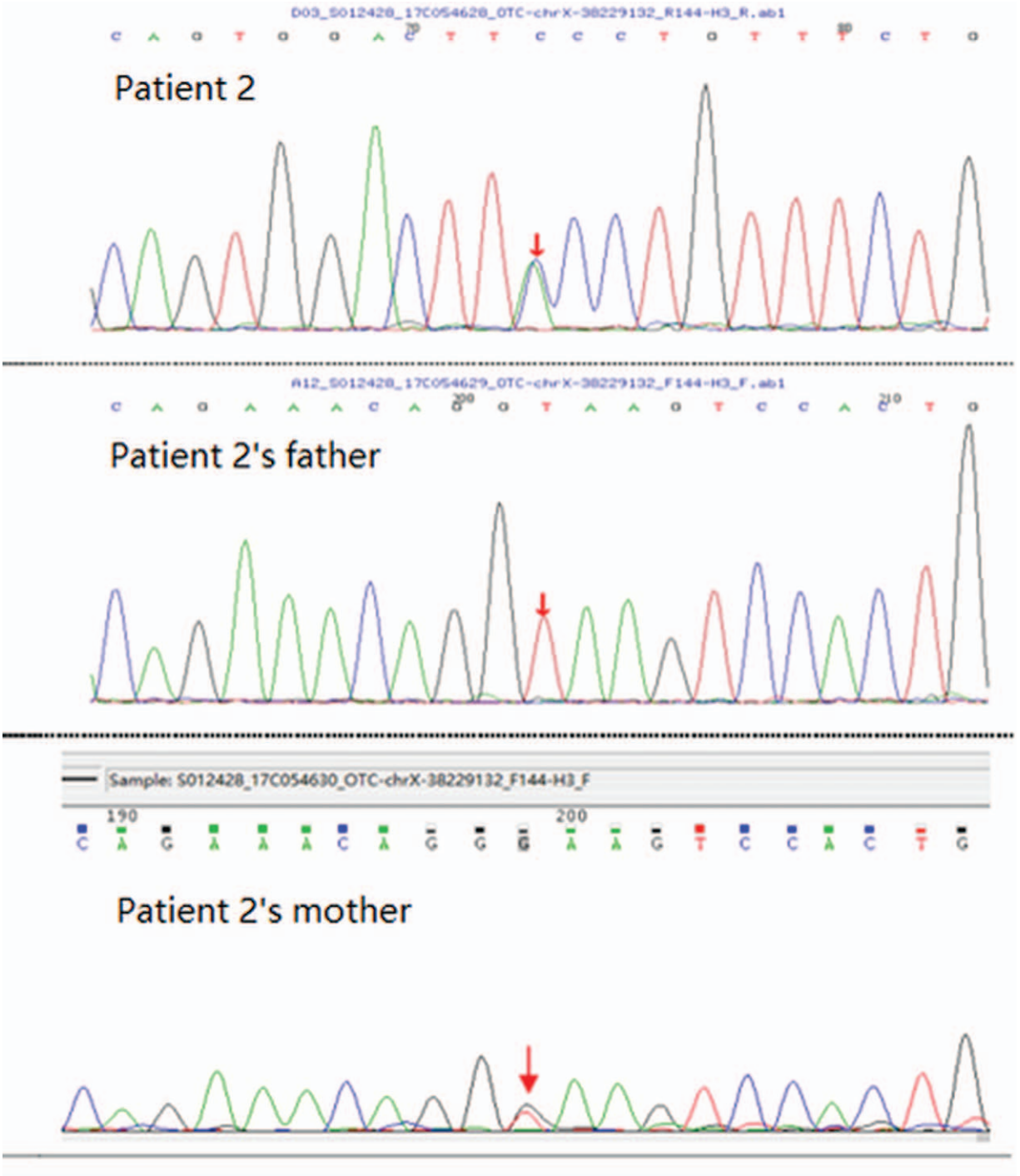

Figure 5. Patient 2's pedigree analysis.

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Software: Guoyan Lu, Fumin Zhao.
Supervision: Fumin Zhao.
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References

[1] Pizzi MA, Alejos D, Hasan TF, et al. Adult presentation of ornithine transcarbamylase deficiency: 2 illustrative cases of phenotypic variability and literature review. Neurohospitalist 2019;9:30–6.

[2] Shao Y, Jiang M, Lin Y, et al. Clinical and mutation analysis of 24 Chinese patients with ornithine transcarbamylase deficiency. Clin Genet 2017;9:318–22.

[3] Chongsrisawat V, Damrongphol P, Ittiwut C, et al. The phenotypic and mutational spectrum of Thai female patients with ornithine transcarbamylase deficiency. Gene 2018;679:337–81.
[4] Choi JH, Lee BH, Kim JH, et al. Clinical outcomes and the mutation spectrum of the OTC gene in patients with ornithine transcarbamylase deficiency. J Hum Genet 2015;60:501–7.
[5] Batshaw ML, Tuchman M, Summar M, et al. A longitudinal study of urea cycle disorders. Mol Genet Metab 2014;113:127–30.
[6] Gao J, Gao F, Hong F, et al. Hyperammonemic encephalopathy in a child with ornithine transcarbamylase deficiency due to a novel combined heterozygous mutations. Am J Emerg Med 2015;33: 474.e1–3.
[7] Alameri M, Shakra M, Alsaadi T. Fatal coma in a young adult due to late-onset urea cycle deficiency presenting with a prolonged seizure: a case report. J Med Case Rep 2015;9:267.
[8] Han F, Han L, Ye J, et al. Clinical characteristics and analysis of mass spectrometric data in patients with ornithine transcarbamylase deficiency. Zhonghua Yi Xue Za Zhi 2014;94:2684–6.
[9] Lee JH, Kim GH, Yoo HW, et al. OTC gene in ornithine transcarbamylase deficiency: clinical course and mutational spectrum in seven Korean patients. Pediatr Neurol 2014;51:354–9. e1.
[10] Kido J, Kawasaki T, Mitsubuchi H, et al. Hyperammonemia crisis following parturition in a female patient with ornithine transcarbamylase deficiency. World J Hepatol 2017;9:343–8.
[11] Yamaguchi S, Brailey LL, Morizono H, et al. Mutations and polymorphisms in the human ornithine transcarbamylase (OTC) gene. Hum Mutat 2006;27:626–32.
[12] Caldovic L, Abdikarim I, Narain S, et al. Genotype-phenotype correlations in ornithine transcarbamylase deficiency: a mutation update. J Genet Genomics 2015;42:181–94.
[13] Tong W, Jin D, Sun J. Report of a case with late-onset ornithine transcarbamylase deficiency with gas chromatography-mass spectrometry and DNA sequencing confirmation and literatures review. Zhonghua Er Ke Za Zhi 2015;53:366–9.
[14] Gropman A. Brain imaging in urea cycle disorders. Mol Genet Metab 2010;100(Suppl 1):S20–30.
[15] Takanashi J, Barkovich AJ, Cheng SF, et al. Brain MR imaging in neonatal hyperammonemic encephalopathy resulting from proximal urea cycle disorders. AJNR 2003;24:1184–7.
[16] Crowe L, Anderson V, Hardikar W, et al. Cognitive and behavioural outcomes of paediatric liver transplantation for ornithine transcarbamylase deficiency. JIMD Rep 2018;97.