A case report of two siblings with hypertyrosinemia type 1 presenting with hepatic disease with different onset time and severity

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ABSTRACT

Hereditary tyrosinemia type 1 (HT1) is an autosomal recessive disorder caused by a defect in fumarylacetoacetate hydroxylase (FAH) encoded by the FAH gene. Patients with HT1 disorder present with increased blood tyrosine, succinyl acetoacetate, and succinyl acetone levels, and develop clinical manifestations including liver failure, kidney tubular dysfunction, growth failure, rickets, pseudo-porphyric crises, and hepatocellular carcinoma. We encountered two siblings with HT1. Among the siblings, the elder brother developed acute liver failure with coagulopathy at the age of 2 months and was rescued by liver transplantation (LT) following combination therapy with continuous hemodiafiltration and plasma exchange. The younger sister was followed up from the prenatal period for signs of HT1 due to prior history of the condition in her sibling. She was initially considered a carrier of HT1 owing to the lack of overt signs of the disease and negative urine screening for succinyl acetone (SA). She was eventually diagnosed with HT1 because of liver disorder at 9 months of age, associated with a positive urine SA result. Her disease state was controlled by treatment with nitisinone (NTBC). DNA analysis of both siblings identified heterozygous status for a previously reported FAH pathogenic allele (c.782C > T) and a novel likely pathogenic variant (c.688C>G). The siblings have stable lives with no developmental delay or impaired growth. NTBC treatment is effective in preventing the progression of liver and kidney diseases. However, even in cases treated without LT, clinicians should follow up the clinical outcomes over long term, as patients may require LT when developing complications, such as hepatocellular carcinoma.

1. Introduction

Hereditary tyrosinemia type 1 (HT1, OMIM276700) is an autosomal recessive disorder caused by a defect in fumarylacetoacetate hydroxylase (FAH, EC: 3.7.1.2), which catalyzes the last step of the tyrosine degradation pathway converting fumarylacetoacetate into fumarate and acetoacetate. In HT1, blood tyrosine, succinyl acetoacetate, and succinyl acetone (SA) levels are increased [1,2], and clinical manifestations, including liver failure, kidney tubular dysfunction, growth failure, rickets, and pseudo-porphyric crises, are often present [3]. Moreover, patients with untreated HT1 may develop hepatocellular carcinoma (HCC) [4,5]. The global incidence of HT1 is estimated to be 1/100,000–1/200,000 [1,6]. However, the incidence of HT1 is extremely low in Japan compared to the global incidence [7].

The treatment for HT1 is restriction of tyrosine and phenylalanine intake. Plasma tyrosine concentrations should be maintained between 200 and 400 μmol/L [8]. Nitisinone (2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione, NTBC), an inhibitor of 4-hydroxyphenylpyruvate dioxygenase, suppresses the production of SA and related neurotoxic and hepatotoxic metabolites and can prevent the progression of liver failure, cirrhosis, and HCC. However, if patients with HT1 develop liver failure and/or HCC, they will require liver transplantation (LT). Ten percent of HT1 patients with acute liver failure (ALF) respond poorly to NTBC treatment and require LT [9].

Abbreviations: ALF, acute liver failure; CHDF, continuous hemodiafiltration; FAH, fumarylacetoacetate hydroxylase; FFP, fresh frozen plasma; LT, liver transplantation; HCC, hepatocellular carcinoma; HT1, hereditary tyrosinemia type 1; NBS, newborn mass screening; NTBC, nitisinone; PE, plasma exchange; PT, prothrombin time; SA, succinyl acetone; SD, standard deviation.

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We encountered two siblings with HT1. Among the siblings, the elder brother developed ALF with coagulopathy and was rescued by LT following combination therapy with continuous hemodiafiltration (CHDF) and plasma exchange (PE). The younger sister was followed up since she was suspected of HT1 before birth. She was considered a carrier of a pathogenic variant in HT1 owing to the absence of clinical signs at the age of 2 months. However, she developed clinical manifestations of HT1 at the age of 9 months. Herein, we present the clinical courses of the two siblings with HT1 and discuss the differences in their clinical courses.

2. Case description

2.1. Case 1

A 51-day-old male infant presented with poor sucking, abdominal distension, and testicular edema. He was the first child of non-consanguineous parents. His father was healthy and his mother had a history of atrial septal defect. He was born without complications at 39 weeks and 6 days, was 50 cm (+0.49 standard deviation (SD)) in length, and weighed 3168 g (+0.38 SD). Newborn mass screening (NBS) using tandem mass spectrometry revealed no abnormalities. He was referred to a local general hospital owing to the development of ascites, liver atrophy, and liver tumor (Supplemental data 1A), and was suspected of liver failure resulting from an inherited metabolic disorder. He received mitochondrial rescue therapy including vitamin B1, carnitine, and co-enzyme Q10. Moreover, fresh frozen plasma (FFP), antithrombin III, albumin, and vitamin K were administered because of a coagulation disorder. However, treatment for liver failure and the coagulation disorder did not lead to a significant improvement. The patient was transferred to our institution because of the need for LT.

He appeared sick, presented with drowsiness, and was jaundiced with the following vital signs: body temperature, 39.7 °C; blood pressure, 140/125 mmHg; respiratory rate, 35 breaths/min; pulse, 190 bpm at a regular cardiac rhythm; and oxygen saturation, 90% with oxygen at 2 L/min. Subcutaneous hemorrhage and purple spots were seen scattered from the hypogastric region to the scrotum. He was intubated and his breathing was managed with a ventilator.

Laboratory tests revealed anemia (hemoglobin: 7.1 g/dL), thrombocytopenia (platelets: 9.6 × 10^4/μL), hypoproteinemia (total protein: 4.6 g/dL), and coagulopathy (prothrombin time (PT): 32.6 s (reference: 11.0–15.2 s), PT-international normalized ratio: 2.73 and activated partial thromboplastin time: 51.4 s (reference: 25.2–35.2 s)). Liver function tests revealed unconjugated hyperbilirubinemia (total...
bhillirubin: 3.2 mg/dL, direct bilirubin: 0.8 mg/dL. The blood alpha-fetoprotein (AFP) level was very high (196,931.0 ng/mL) (Fig. 1).

Administration of FFP, antithrombin III, albumin, and vitamin K was continued. The patient underwent combination therapy with PE and CHDF, and ascitic fluid was removed using continuous drainage (Fig. 1). Moreover, he received antibiotic therapy with aminobenzylpenicillin and clindamycin following ceftriaxone sodium hydrate and vancomycin.

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Urine organic acid analysis demonstrated significantly increased levels of SA and tyrosine metabolites (p-hydroxyphenyl lactic acid [PHPLA] and p-hydroxyphenylpropionic acid [PHPPA]). Moreover, the analysis revealed increased levels of lactic acid, pyruvic acid, phenylactic acid, phenylpyruvic acid, and phenylacetic acid. Blood amino acids analysis showed increased methionine (448.0 μmol/L [reference value: 40.4–90.3 μmol/L]), tyrosine (205.9 μmol/L [reference value: 18.9–40.5 μmol/L]), and phenylalanine (115.2 μmol/L [reference control: 42.6–75.7 μmol/L]) levels. He was diagnosed with HT1 and received NTBC (2 mg/kg/day) and tyrosine- and phenylalanine-free formula. NTBC treatment lowered blood AFP levels (36,252.0 ng/mL and 11,386.0 ng/mL at 2 days and 6 days after NTBC treatment, respectively). However, the coagulation disorder showed no signs of improvement. The liver mass in segment VI showed a tendency to expand, and other multiple masses appeared in the liver. He underwent living donor LT from his mother and was recovered from ALF. Blood gene analysis revealed compound heterozygous mutations NM_000137.4(FAH):c.565G>T (p.Pro261Leu) (a previously reported pathogenic variant allele), c.565G>A (p.Val189Ile), and c.688C>G (p.Leu230Val) (novel likely pathogenic variant) in FAH. In addition, NM_000137.4(FAH):c.565G>A (p.Val189Ile) (a previously reported likely nonpathogenic allele) was also identified (Fig. 2). The patient was definitively diagnosed with HT1. After receiving LT, the NTBC dose was gradually decreased. Since the urine SA was positive once the administration of NTBC was discontinued and renal tubulopathy was not present, a small dose of NTBC (0.15 mg/kg/day) was continued, leading to negative urine SA. At the age of 2 years, his developmental quotient (DQ) on the Enjoji Scale of Infant Analytical Development was normal (motor DQ: 110, sociality DQ: 98, and language DQ: 90). At age of 3 years and 6 months, the plasma tyrosine and phenylalanine levels were 623.0 and 59.1 μmol/L, respectively, while he received NTBC treatment (0.15 mg/kg/day) without restriction of tyrosine and phenylalanine intake. At the age of 5 years and 7 months, he has a stable life without kidney disease, impaired intelligence and growth (height: 107.0 cm (−0.77 SD), weight: 19.0 kg (+0.12 SD)).

2.2. Case 2

Case 2 was the younger sister of Case 1. She was born without complications at 40 weeks and 3 days of gestation, was 50 cm (+0.77 SD) in length, and weighed 3656 g (+1.60 SD). The SA level in the amniotic fluid at 16 weeks’ gestation was 0.13 μmol/L (ten times less than those of patients with HT1, although ten times higher than those of healthy controls). The infant was treated at the neonatal intensive care unit for neonatal hypoglycemia and discharged at the age of 7 days. NBS showed mildly increased methionine levels in the dried blood spots. Postnatal urine examination for organic acids did not show increased SA levels and blood tests revealed no abnormalities (Supplemental data 2). She was considered an obligate carrier of HT1 because she did not present any signs or symptoms related to HT1 at the age of 2 months. She was considered an obligate carrier of HT1 because she did not present any signs or symptoms related to HT1 at the age of 2 months. She was considered an obligate carrier of HT1 because she did not present any signs or symptoms related to HT1 at the age of 2 months. She was considered an obligate carrier of HT1 because she did not present any signs or symptoms related to HT1 at the age of 2 months. She was considered an obligate carrier of HT1 because she did not present any signs or symptoms related to HT1 at the age of 2 months. She was considered an obligate carrier of HT1 because she did not present any signs or symptoms related to HT1 at the age of 2 months. She was considered an obligate carrier of HT1 because she did not present any signs or symptoms related to HT1 at the age of 2 months.

At the age of 9 months, the child was brought to a local general hospital because of changes in skin color and rashes. Blood tests showed mild liver disorder (aspartate aminotransferase, 61 IU/L; alanine aminotransferase, 41 IU/L; lactate dehydrogenase, 418 IU/L; γ-glutamyl transpeptidase, 134 IU/L; cholinesterase, 191 IU/L; type IV collagen, 607
μidemia (total cholesterol: 292 mg/dL, low-density lipoprotein cholesterol: 188 mg/dL, triglyceride: 100 mg/dL), and elevated methionine (254.1 μmol/L) and tyrosine (464.9 μmol/L) levels. Ultrasonography revealed a regenerating 14-mm nodule-like mass. She visited our hospital again with suspected HT1. She did not develop jaundice, hyperammonemia, coagulation disorder, or electrolyte imbalance. Abdominal ultrasonography and contrast-enhanced MRI revealed dull edges and irregular rough surfaces of the liver, which indicated the possibility of hepatic cirrhosis. Multiple masses in the liver were considered regenerating nodules (Supplemental data 1B and 3). The patient was clinically diagnosed with HT1 and received NTBC treatment (1 mg/kg/day). Urine organic analysis revealed high levels of PHPLA, PHPPA, and succinyl acetocetate. At 10 days and 2 months after NTBC treatment, the AFP level was ameliorated to 2380 ng/mL and 82.4 ng/mL. The NTBC dose was increased to 12 mg/day (2 mg/kg/day) from the first dose of 4 mg/day (1 mg/kg/day). She was definitively diagnosed with HT1 owing to the detection of the same mutations in the FAH gene as her brother (Fig. 2). At the age of 2 years and 6 months, she has a stable life without kidney injury, developmental delay, or growth delay (height: 88.5 cm (-0.04 SD), weight: 13.5 kg (0.96 SD)). The urine SA was negative (0.1 μg/mgCr; control <0.5) after receiving NTBC (1 mg/kg/day) and tyrosine and phenylalanine-free formulas.

3. Discussion

We present a report of two siblings with HT1 presenting with different clinical courses. Among the siblings, the elder brother was diagnosed with HT1 owing to the development of ALF, and the younger sister was diagnosed with HT1 owing to a skin rash and liver lesion despite careful follow-up until 2 months after birth. The older brother was rescued by LT following the combination therapy with PE and CHDF and continued receiving a low amount of NTBC after LT. The younger sister was managed with NTBC and tyrosine and phenylalanine-free formulas. They have a stable life without impaired intelligence or development.

Blood SA level is recommended as the primary marker to detect patients with HT1 in the NBS using the dried blood spots but not tyrosine. It is recommended to measure blood or plasma SA at the time of diagnosis and during follow-up and not urine SA according to an US and Canadian consensus group [4]. However, in Japan, tyrosine is used as a marker of HT1 in the NBS, and urine SA is measured at the time of diagnosis and during follow-up. No institution in Japan measures blood or plasma SA. Therefore, we need to develop a system to measure blood or plasma SA because only measuring urine SA may increase the risk of delayed appropriate diagnosis and treatment for patients with HT1. LT is an effective definitive therapy for HT1 with ALF [10,11], which can be expected to restore liver function and reduce the risk of HCC [12]. In a review of 125 patients with HT1 in the United Network for Organ Sharing database, the 1- and 5-year survival outcomes were >90% [12]. Urine and plasma SA levels decreased but were not completely suppressed owing to continued production in the kidneys [13]. Case 1 also continued receiving a small amount of NTBC after LT, owing to positive urine SA on discontinuation of NTBC and presented negative urine SA after restarting NTBC. The continued use of NTBC at a lower dose after LT may be recommended to protect renal function, although further accumulation of data showing the renal protective effect is required [14].

Case 2 was treated by administration of NTBC and tyrosine and phenylalanine-free formulas. Low plasma NTBC concentrations are reported to be associated with a higher risk of severe complications, including growth failure, later transplantation, and learning difficulties, despite undetectable urinary SA levels [15]. Therefore, it is necessary to follow the plasma NTBC concentration in case 2 in the future, although she has a stable life without any complications.

Neurodevelopmental impairment is a major issue in patients with HT1, even when they are managed with good metabolic control. Neurodevelopmental impairment includes a lower developmental or intelligence quotient, impaired executive functioning, motor abilities, social cognition, and schooling problems [16–18]. García et al. reported a significant correlation between the phenylalanine/tyrosine ratio and intelligence quotient at school age [19]. HT1 patients with early onset of symptoms could be at risk for progressive cognitive functional decline over time. Therefore, it was suggested that even patients with HT1 receiving NTBC and a protein-restricted diet may have developmental delay and impaired intelligence. Fortunately, the siblings have not presented with developmental delay or impaired intelligence.

The siblings presented with compound heterozygous variants of c.565G > A, c.688C > G, and c.782C > T in the FAH gene. We summarized the variants previously detected in patients with HT1 (Supplemental datas 4 and 5). c.782C > T has previously been reported as a pathogenic variant. c.565G > A has been reported as a conflicting interpretation of the pathogenicity variant, and c.688C > G has not been reported previously. In this case, c.688C > G was a variant derived from the mother and a novel pathogenic variant. The c. 565G > A and 782C > T variants were derived from the patient’s father. The c.782C > T variant is a missense mutation [20], which was detected in Ashkenazi-Jewish patients with HT1 examined in Israel [21] and also reported in Saudi Arabia and Egypt. [22]

Patients with HT1 are likely to have weak genotype-phenotype correlations and there are reported variabilities in phenotypes (onset of clinical disease and severity) with identical genotypes. In a report by Couce et al. [23], 16 patients with a homozygous variant of c.554-1G > T (IVS6-1G > T) had a median diagnosis time of 134 days (IQR: 22–270). Eight patients presented with acute onset manifestations <6 months after birth, and four and two patients developed subacute onset manifestations over 6–24 months and chronic onset manifestations >24 months, respectively. Five patients developed ALF, and only one patient presented with cognitive impairment. Here also, our siblings demonstrated variability in presentation and without a clear genotype-phenotype correlation in that their clinical onset time and hepatic manifestations, including the need for liver transplantation, differed.

This study was approved by the institutional ethics committee of the Faculty of Life Science, Kumamoto University (Genome No. 414). Written informed consent was obtained from the parents of the patients.

4. Conclusion

We presented a report of two siblings with HT1 who developed liver manifestations with different onset times and severities. Both harbored a novel pathogenic variant. They are currently living stable lives without developmental delay or impaired growth. NTBC treatment is effective in preventing the progression of liver and kidney diseases. Moreover, even in cases treated without LT, clinicians should follow up their outcomes for an extended period, and they may need LT when developing complications, such as HCC.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest related to this study.
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2022.100892.