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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Changes in the palms and soles. (a–c) Reddening and indurative edema on day 21; (d,e) peeling of the skin on day 25.

Table S1. Clinical course of the present case.

Discontinuation of NTBC after liver transplantation in tyrosinemia type 1

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Key words 2-(2-nitro-4-trifluoromethylbenzoyl)-1-3-cyclohexanedione, hereditary tyrosinemia type 1, liver transplantation.

The management of hereditary tyrosinemia type 1 (HT1) has been revolutionized by the introduction of 2-(2-nitro-4-trifluoromethylbenzoyl)-1-3-cyclohexanedione (NTBC).[1] Continued NTBC treatment after liver transplantation (LT) has been suggested as a means of controlling renal succinylacetone (SA) production and hence improving long-term renal function.[2] A factor to consider is that even low-dose NTBC causes significantly raised tyrosine,[2] raising the issue of whether reintroduction of dietary restriction would be necessary. Furthermore, some patients with HT1 treated with NTBC and protein-restricted diet are at risk of developmental delay and impaired cognitive functioning.[1] We describe here the case of a HT1 patient who was allowed an unrestricted diet without NTBC after living-related donor LT.

The male patient was the younger of two children of non-consanguineous Japanese parents. The pregnancy, neonatal period, and family history were unremarkable. He was asymptomatic until presentation with abdominal distension and growth retardation aged 1 year and 4 months. He was found to have mild hepatosplenomegaly and anemia (hemoglobin, 7.4 g/dL). Thrombocytopenia (platelets, 71 $\times$ 10^9/L) was present. Prothrombin time (41.8%) and activated partial thromboplastin time (45.1 s) were also abnormally prolonged. Elevation of aminotransferases was mild and hyperbilirubinemia was not present. Serum α-fetoprotein (AFP) was increased at the time of admission (148 080 ng/mL). Multiple liver nodules were detected on abdominal computed tomography (CT) and magnetic resonance imaging (MRI; Fig. 1). They were hyperintense on T1-weighted MRI and hypointense on T2-weighted MRI (Fig. 1c,d). The patient had renal tubular dysfunction with a Fanconi syndrome resulting in phosphaturia with hypophosphatemia and rickets, glycosuria, generalized aminoaciduria, hyperchloremic metabolic acidosis and hypouricemia. Plasma tyrosine, methionine and phenylalanine at onset were 628 nmol/mL (normal, 40.4–90.3 nmol/mL), 324 nmol/mL (normal, 18.9–40.5 nmol/mL) and 242 nmol/mL (normal, 42.6–75.7 nmol/mL), respectively. SA in dried blood spots was 19.2 nmol/mL (controls, <5 nmol/mL) and urinary SA was 14.0 mmol/mL (controls, <4 mmol/mL). These data confirmed HT1, and NTBC combined with a low-tyrosine and -phenylalanine diet were commenced. All biomarkers of renal tubular dysfunction normalized in the first 2 weeks of NTBC therapy. Urinary SA decreased to 1.1 mmol/mL at 2 months after NTBC initiation. The patient had a logarithmic decrease in AFP, but which failed to completely normalize. It is difficult to rule out the malignant potential of nodules. Although

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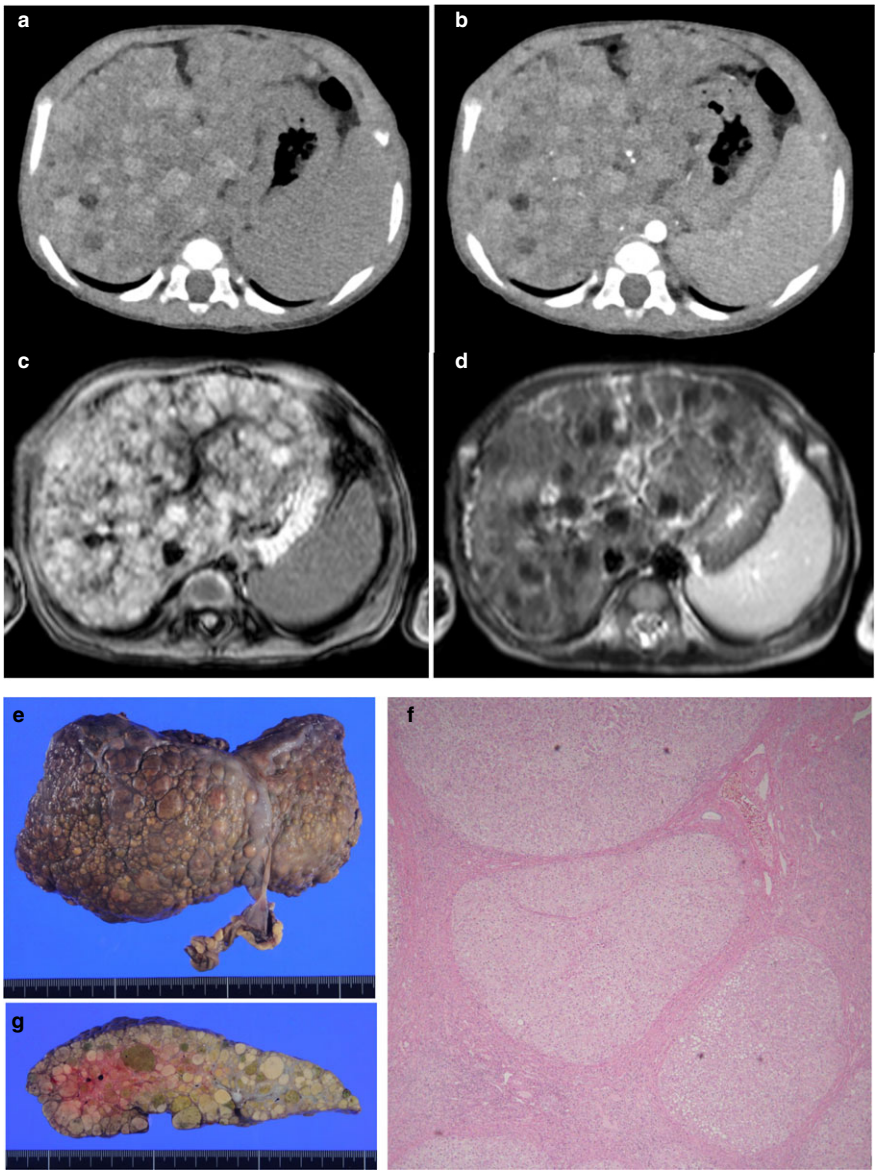

Fig. 1 (a) Plain and (b) enhanced computed tomography and (c) T1-weighted and (d) T2-weighted magnetic resonance imaging in a 1-year-old boy with multiple liver nodules and cirrhosis, leading to the diagnosis of hereditary tyrosinemia type 1 (HT1). (e–g) Liver pathology specimen of HT1. (e,g) Explanted liver showing extensive macronodular cirrhosis. (f) Hematoxylin and eosin stain of liver tissue. The non-neoplastic liver parenchyma showed inactive cirrhosis that was morphologically cryptogenic.

postoperative complications such as non-functioning of the graft and life-long immunosuppression were seen, the patient underwent living-related donor LT aged 1 year and 8 months. Malignancy was not discovered in the explanted liver. SA in the dried blood spots was 0.5 nmol/mL and urinary SA was 0.9 mmol/mL at 1 month after transplantation. Therefore, the patient was allowed an unrestricted diet plus the withdrawal of NTBC after LT. Plasma tyrosine, methionine and phenylalanine at 1 year after LT were 125, 35 and 70 nmol/mL, respectively. Although the patient has received tacrolimus after transplantation, renal function remains normal. The patient's developmental quotient was 100 on the Enjoji scale at the age of 2 year and 11 months. Genetic analysis for definite diagnosis was not performed due to lack of parental consent.

The incidence of HT1 is around 1:100 000–125 000 births worldwide. Although the exact incidence of HT1 in Japan is still unknown, five cases of HT1 have been reported.[3] One patient died because of hepatic coma and three out of five received LT.[3] Patients on NTBC and diet, without liver nodules are not considered to be candidates for LT.[2] LT, however, is a good option for the treatment of HT1 patients developing liver nodules, with a high suspicion of malignancy.[2] HT1 is categorized into three main clinical types (acute, subacute and chronic) based on the age of onset and the clinical

manifestations.[4] The present patient had the chronic type with slow progression and may have had a relatively high residual enzyme activity. Therefore, even on discontinued NTBC after LT, the patient may be in good condition without medical problems. Decrease of fumarylacetoacetate hydrolase activity in HT1, however, causes the accumulation of maleylacetoacetate and fumarylacetoacetate, and of their derivatives, SA and succinyl acetoacetate (SAA). These toxic metabolites are responsible for severe disruption of intracellular metabolism of the liver and kidney. LT is essentially curative but does not fully correct metabolic perturbations in HT1 because kidneys continue to excrete SAA and SA in urine.[4] Residual urinary SA excretion after LT has been reported, suggesting a potential contribution to the progression of renal dysfunction.[5] Here, we have described a case of mild-type HT1 that resulted in discontinuation of NTBC owing to improved metabolic condition after LT. It is unknown, however, whether NTBC treatment after LT can be stopped in patients with mild-type HT1. A larger series of patients comparing discontinuation with continuation of NTBC after LT is therefore necessary in order to address this question.

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Disclosure

The authors declare no conflict of interest.

Author contributions

K.K. and H.T. contributed to the conception and design of this study; K.K. and K.A. diagnosed and treated the patient; M.I., K.U. and H.S performed liver transplantation; A.H. critically reviewed histopathology; K.K. and H.T. wrote the manuscript; M.H. critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

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Efficacy of ketogenic diet for pyruvate dehydrogenase complex deficiency

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Key words ketogenic diet, mitochondrial disease, pyruvate dehydrogenase complex deficiency.

Pyruvate dehydrogenase complex (PDHc) is a multi-enzyme complex that decarboxylates pyruvate and supplies acetyl-coenzyme A (acetyl-CoA) to the tricarboxylic acid cycle to produce adenosine triphosphate. Thus, PDHc deficiency is a mitochondrial disorder commonly associated with conditions such as lactic acidosis and progressive neuromuscular degeneration during childhood.[1] In terms of treatment, thiamine, vitamin cocktails, anti-epileptic drugs, and nutritional treatment are available, but these treatments have limited efficacy. The ketogenic diet (KD) can be used in inherited metabolic disorders, including PDHc deficiency, in two different ways: first, to target the underlying metabolic condition by bypassing the metabolic fault; and second, to treat clinical symptoms of the inherited metabolic disorder, such as seizure/epilepsy.[2] We previously presented a case of a novel mutation (R263X) of the E1α subunit in PDHc deficiency.[3] Herein, we report the clinical course, especially after the introduction of KD.

The present patient was a Japanese girl who had intrauterine growth retardation, fetal cerebral ventriculomegaly, seizure, and lactic acidosis beginning in the neonatal period. After diagnosis, her main nutrition was modified to medium

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