A patient with urinary succinylacetone-negative hereditary tyrosinemia type 1

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The patient was born uneventfully at a gestational age of 37 weeks and 3 days. Her weight and length at birth were 2926 g and 50.5 cm, respectively. All marker values were below the cut-off levels during newborn screening, and succinylacetone (SA) was not measured. No abnormalities were noticed at the 1 month well-baby visit. She had a cough 3 weeks prior to admission, which worsened 4 days before admission. She visited the hospital and was referred to our hospital for suspected biliary atresia at 2 months of age. Blood examination on admission revealed elevated liver enzyme, abnormal coagulation, high alkaline phosphatase, hypoalbuminemia, anemia, thrombocytopenia, cholestasis, marked elevated alpha-fetoprotein (AFP), acidemia, and high levels in lactic acid. Abdominal ultrasound revealed the gallbladder, ruling out biliary atresia (Supporting Information, Figure S1A). Abdominal computed tomography (CT) showed ascites, but no fatty liver and right lobe atrophy was suspected (Supporting Information, Figure S1B). Fresh frozen plasma transfusion was required every day. She was hospitalized during the New Year holiday and could not be tested for her metabolic disorders. Thus, based on clinical symptoms, we considered her citrin deficiency and started medium chain triglyceride (MCT) milk. However, her abnormal coagulation did not improve after starting MCT milk. Metabolic tests were performed on the eighth day of hospitalization. On the 14th day of hospitalization, an allergic shock occurred during a platelet transfusion. The next day, she was ventilated due to alveolar bleeding. On that day, we received the test result, showing her high blood tyrosine level, but her urinary SA was 0.3 mmol/mol Cr (reference < 4) measured using liquid chromatography-tandem mass spectrometry (LC–MS/MS). Serum SA concentration was measured to rule out hereditary tyrosinemia type 1 (HT1). The patient's serum SA (0.78 μM) was slightly elevated (cut-off level is 1.0 μM, but those in normal babies are usually less than 0.1 μM). On the 18th day of hospitalization, she died of respiratory failure (Figure 1). After death, a percutaneous liver needle biopsy and a genetic analysis were performed. Genetic testing identified a compound heterozygous mutation, NM_000137.4:c.[782C>T];[1210G>A] in the FAH gene, which was previously reported as pathogenic.1

Hereditary tyrosinemia type 1 (OMIM 276700) is an autosomal recessive disease caused by a defect in fumarylacetoacetate hydratase.2 As a result, toxic metabolites, such as SA, accumulate. Serum or urine SA levels are used as a diagnostic marker in the US and Canada.3 As a result, toxic metabolites, such as SA, accumulate. Serum or urine SA levels are used as a diagnostic marker in the US and Canada.3 as tyrosine is neither sensitive nor specific for HT1. In Japanese guideline, elevated urinary SA is a diagnostic marker of HT1. However, urinary SA levels were within the normal range in this patient. Serum SA was slightly elevated but below the cut-off level. Previously we encountered a patient with HT1 who had advanced liver failure. His serum SA level was 2.58 μM at diagnosis at...
5 months of age but it was 28.7 μM in the neonatal dried blood spot. Further, SA was not elevated in patients with liver failure. Based on these findings, the lack of SA elevation could be attributed to liver failure. Mass screening using blood SA may not be realistic in terms of cost in Japan, where the frequency of HT1 is low. However, if this patient had undergone mass screening for HT1 by using blood or urine SA, she would have had a positive result. The blood SA level in the neonatal dried blood spot was high at 5.5 μM in the present case. Despite being considered a severe phenotype of the genetic variant, the SA level was not proportionally high. This could be due to a lack of strict correlation between genotype and phenotype in HT1. Finally, a genetic diagnosis was made for this patient. The parents are planning the next child. A genetic test is therefore beneficial not only for proband diagnosis but also for prenatal diagnosis.

We encountered a girl with urinary SA-negative HT1 who died following liver failure. However, serum SA was slightly elevated, and the final diagnosis was made through a genetic test. Blood and urine SA are useful diagnostic markers for HT1. However, they might decrease as liver failure progress, making diagnosis difficult in Japan, where mass screening does not include blood SA.

**AUTHOR CONTRIBUTIONS**

Jun Mori, Taizo Furukawa and Kazuki Kodo attended to the patient. Jun Mori wrote the manuscript; Miori Yuasa and Yosuke Shigematsu measured succinylacetone. Jun Mori, Hisakazu Nakajima, Mitsuru Kubota and Yosuke Shigematsu gave conceptual advice. All authors have read and approved the final manuscript.

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**CONFLICT OF INTEREST STATEMENT**

The authors declare no conflicts of interest.

**INFORMED CONSENT**

We obtained informed consent to publish this article from the parents of the patient.

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**REFERENCES**


SUPPORTING INFORMATION

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