A girl was born at 37+4th gestation week in our hospital. She had no previous familial medical history of inherited metabolic disorder or other congenital disease. At birth, she had a pulse rate of 160/min, respiratory rate of 56/min, and body temperature of 37.2°C. Her Apgar scores were both 10 at 1 minute and 5 minutes after birth. Intermittent vomiting and irritability was observed just after birth, and she was therefore given intravenous hydration of 5% dextrose solution and observed closely. At 48 hours after birth, tandem mass spectrometry was done for neonatal screening and showed increased blood levels of C5 isovalerylcarnitine and ammonia (180 \( \mu \)mol/L). Also, in urine organic acid analysis, it was found that isovalerylglycine was greatly increased to 2,049 mmol/mol creatinine (Cr, reference value: < 5 mmol/mol Cr) as well as lactic acid to 670 mmol/mol Cr (reference value: < 150 mmol/mol Cr). Based on the results above, the patient was diagnosed with isovaleric acidemia (IVA) and mutation study of IVD gene was performed. As a result of this analysis, we found out that c.129T>G (p.Asn43Lys) and c.1033A>G(p.Asn345Asp) mutations existed as heterozygosity at Exon 1 and Exon 10 respectively, and both the mutations were novel ones as previously reported by Kim et al., [1]. After being diagnosed with IVA, she was started on a leucine restriction diet and received supplementary intake of both carnitine (100 mg/kg/day) and glycine. With this special diet and supportive medications, we observed that blood ammonia level gradually lowered to normal level (45 \( \mu \)mol/L) and isovalerylglycine level in urine also decreased. During this time, her complete blood counts (CBC) showed the normal levels of hemoglobin (Hb), platelet counts, and mean corpuscular volume (Table 1).

After discharge, she showed sustained normal levels of isovalerylglycine and lactate in urine, associated with good weight gain and general status with no abnormal symptom. Although decreased Hb levels of 10.6 and 8.5 g/dL were observed twice in the outpatient clinic, suggesting progressive anemia, she was closely followed up under the impression of physiologic anemia of newborn without further evaluation or management.

On about day 60 after birth, she visited our hospital again via the emergency department because of fever up
to 38.1°C. Her CBC on hospitalization showed Hb 6.9 g/dL, and re-examination on the next day also showed worsening of anemia of Hb 6.6 g/dL with reticulocyte count of 1.88%, despite normal white blood cell & platelet count (Table 1).

She received red blood cell (RBC) transfusion of 10 mL/kg. Further evaluation of her anemia showed that serum iron and total iron-binding capacity (TIBC) was 33 μg/dL and 139 μg/dL respectively, and plasma ferritin level was 156.3 ng/mL, which are inconsistent with iron deficiency anemia (IDA). Furthermore, normal total and direct bilirubin levels (0.21 mg/dL and 0.14 mg/dL) indicated that there was no evidence of acute hemolysis. After having a febrile seizure attack, further work up was performed and both her cerebrospinal fluid examinations and magnetic resonance imaging of brain showed normal results. We concluded a diagnosis of simple febrile convulsion associated with systemic viral infection, and she recovered after receiving fever control and supportive care. After RBC transfusion, her Hb level improved to 13.6 g/dL. Despite the lack of evidence for IDA, we started her on supplementary oral iron agent to her after discharge for 1 month. However, when she was later hospitalized again with bronchopneumonia caused by metapneumovirus infection at the age of 4 months old, she again showed low Hb counts of 10.5 g/dL and 8.7 g/dL. After RBC transfusion, her Hb level recovered to 12.1 g/dL (Table 1). All other evaluations for her infections showed negative findings in other respiratory viruses, rotavirus, norovirus and enterovirus. While being maintained on IVA management, further follow-up examinations of her Hb in the outpatient clinic showed normal levels (12.4 g/dL and 13.1 g/dL). However, when she was later hospitalized again after a febrile seizure attack and showing positivity for influenza type A at 27 months old, her Hb level was decreased to 10.7 g/dL (Table 1). Her reticulocyte count was 0.51% (with 20.85% of immature reticulocyte fraction) and serum iron and TIBC was 69 μg/dL and 291 μg/dL, with a plasma ferritin level of 57.8 ng/mL, which were inconsistent with IDA. Her haptoglobin (153.3 mg/dL), vitamin B12 (1,750 pg/mL), folate (17.1 ng/mL) levels and peripheral blood smear showed normal findings, indicating no evidence of acute hemolysis or megaloblastic anemia. Her Hb electrophoresis also showed normal Hb fractions for her
age. She was discharged from the hospital after treatment of influenza, and urine organic acid analysis was regularly performed in the outpatient clinic, while continuing her dietary restriction and supplementation of glycine and carnitine.

Various metabolic processes in the body make various kinds of organic acids as intermediate products, which are harmful to the human body after accumulation, but are normally passed out or eliminated through adequate metabolism processes. However, these organic acids cannot be eliminated by a catalyzed enzyme with a quantitative or functional defect, and which accumulation leads to organic acidemia, a kind of inborn error of metabolism. A type of inborn error of metabolism, IVA is caused by a genetic defect of the IVD gene, which is located on chromosome 15q14-15, resulting in functional defect of isovaleryl-CoA dehydrogenase in the mitochondria and abnormal leucine metabolism and accumulation of isovaleric acid in the blood [1, 2]. Patients are usually diagnosed after showing nonspecific symptoms such as vomiting, lethargy or irritability, altered mentality, or severe ketosis [2].

Tandem mass spectrometry performed with routine newborn screening makes detection of inborn errors of metabolism much easier at an early stage, which is crucial for management and patient quality of life. However, although it is well known that some kinds of organic acidemia can be associated with various kinds of organ-specific signs or symptoms besides nonspecific systemic symptoms [1, 2], there is no known study or report of hematological abnormal findings accompanying organic acidemia in Korea.

A study from Turkey found that 44 cases of organic acidemia were associated with various anemias among more than 2,000 cases of inborn error of metabolism. The most common organic acidemia accompanied by anemia was methylmalonic acidemia, and two cases of IVA were also reported to be accompanied by anemia, specifically megaloblastic anemia from vitamin B12 deficiency and chronic hemolytic anemia [3]. Similarly, in a Korean study by Bang et al. [2] using the urine organic acid analyses conducted by our institution, 470 cases among 1,787 consulted specimens were diagnosed with various kinds of organic acidemia and 7 of the 470 cases had anemia before diagnosis. These findings suggest that anemia is an uncommon but not rare problem in organic acidemia. However, most patients with inborn error of metabolism including organic acidemia are diagnosed and managed by pediatric endocrinology/metabolism specialists, and hematological problems can be overlooked because these problems are not common in patients with inborn error of metabolism. Furthermore, as in our case, their hematological problems can be improved with dietary restriction and supplementary medications without metabolic decompensation, before definite presentation of their anemia or other hematological problems. What is also important is that it is unclear whether hematological problems are a direct result of the underlying disease with its decompensation or secondary to other factors, such as infection, medication, or dietary restriction.

There are many reports about organ-specific symptoms or problems of the central nervous system or pancreas, besides well known nonspecific symptoms in children with IVA [4, 5]. Moreover, reports from other countries have reported on neutropenia, thrombocytopenia or leucopenia in children with IVA [1, 4]. These reports suggest that metabolic decompensation by fever, infection or dehydration in IVA patients can result in organ-specific problems beyond nonspecific systemic symptoms. Laboratory findings in our case indicated that there is no evidence of iron deficiency, megaloblastic anemia or other congenital anemia such as hemoglobinopathy, suggesting the possibility of primary anemia by metabolic decompensation of the hematological system. Although some studies showed that long term use of carnitine, an important supplementary medication in IVA management, can result in organ-specific problems without metabolic decompensation in child with IVA, without any other cause of anemia, in Korea.

We have herein presented a case of anemia accompanied by metabolic decompensation of organic acidemia. In collaboration with pediatric endocrinology/metabolism specialists, further investigation into the incidence and mechanisms of anemia that accompanies these inborn errors of metabolism should be performed, along with thorough evaluation and management for this uncommon...
References