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Letter to Editor

Pancytopenia: A Rare Presentation of Late Onset Isovaleric Acidemia

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Dear Editor,

Isovaleric academia was first recognized by Tanaka and colleagues as a new genetic disorder of leucine metabolism in two siblings in early infancy. There is a defect in the catabolism of leucine resulting in the accumulation of isovaleric acid (1). Isovaleric acidemia (IVA) is an autosomal recessive inborn error of leucine metabolism caused by a deficiency of the mitochondrial enzyme isovaleryl-CoA dehydrogenase resulting in the accumulation of derivatives of isovaleryl-CoA. The clinical presentation of IVA is highly variable ranging from severely affected to asymptomatic individuals. It may present in the neonatal period as an acute episode of metabolic acidosis leading to coma and death or later as a chronic intermittent form associated with developmental delay and recurrent acidotic episodes during catabolic phases (2).

A three-year-old boy was admitted with vomiting, lethargy and loss of consciousness after a period of upper respiratory tract infection. The patient was the second child of non-relative parents. Hewas admitted nine months earlier with a similar presentation diagnosed as encephalitis. Upon admission, he was febrile and he had a pulse rate of 110/min and respiratory rate of 52/min. Physical examination was unremarkable for hepatosplenomegaly. Laboratory examination showed severe neutropenia, moderate anemia, and thrombocytopenia and compensated metabolic acidosis.

Biochemical analysis including blood glucose and coagulation profile were within normal limits. Serum C-reactive protein, erythrocyte sedimentation rate and lactate dehydrogenase were normal. Serumammonia level was 110 mcg/dL (19-90). Cerebrospinal fluid and urine analysis showed no abnormality. Blood and cerebrospinal fluid cultures were negative. The results of a complete blood count revealed the following: hemoglobin 8.7 g/dl; platelet count $103x10^9$ /µL; white blood cells$0.8x10^9$/µL; neutrophil 70%; lymphocyte 17%; monocyte 5% and band cells 5%. Arterial blood gas showed pH 7.29; Pco2 27 mmHg; Hco3 13.4 mEq (22-26) with normal Po2 and O2 saturation. Urinary organic acid profile analyzed with Gas Chromatography Mass Spectrometry (GC-MS) revealed excessive excretion of isovalerylglycine (1320 times the normal value).

Due to persistent pancytopenia, bone marrow aspiration was performed which showed ahypocellular marrow with trilineage hematopoiesis and relative monocytosis. Clinical findings of stupor and coma along with metabolic acidosis, mild hyperammonemia and increased excretion of urinary organic acids (isovalerylglycine) all were compatible with IVA. Upon diagnosis, low protein diet, L-carnitineand glycine were prescribed for the patient. After two weeks of treatment, metabolic acidosis resolved and white blood cells and platelets gradually normalized.

On day 14th of admission, laboratorydata showed: WBC 3.6×10^9/µL, hemoglobin 12.8 g/dl; platelet count 462×10^9/µL; pH 7.44; Pco2 37 mmHg and Hco3 25 mEq.

Severe pancytopenia has been previously reported in two infants with IVA. It was suggested that pancytopenia might be due to arrested maturation of hematopoietic precursors (3). There is also a report of IVA in a two-year-old female presenting as diabetic ketoacidosis who demonstrated neutropenia and thrombocytopenia.[4] Varying degrees of cytopenia in organic academia including IVA has been ascribed to the toxic effect of organic acids on hematopoietic cells. Secondary hemophagocytic syndrome has also been reported in IVA (3, 4). A newborn who was admitted at 10 days of age with lethargy, poor feeding, hypothermia, cholestasis and profound pancytopenia expired at 19 days of age. Autopsy showed extramedullary hematopoiesis and myelodysplasia of the bone marrow with arrest of the myeloid series at the promyelocytic stage. The appearance of bone marrow resembled promyelocytic leukemia; however, the 15:17 translocation was not present. The maturation arrest in granulopoiesis in IVA appears to be most likely due to a direct metabolic effect on granulocyte precursor cells (5).

Pancytopenia has been also reported in other types of organic acidemia such as methylmalonic andpropionic academia. Bakshi and co-workers have reported three patients with MMA who presented with severe refractory pancytopenia during the acute illness. Their bone marrow examination revealed a wide spectrum of pathologies varying from bone marrow hypoplasia, hemophagocytosis to myelodysplasia with ring sideroblasts (6).

In a study on 46 children (4-5 years old) with various inherited metabolic disorders, different kinds of anemia were observed. Moreover, bicytopenia or pancytopenia was found in 8 (17.4%) of the children. The study indicated that in organic acidemias including methylmalonic acidemia, propionic acidemia, IVA, and argininosuccinic acidemia, most patients had anemia of chronic disease followed by vitamin B_{12} deficiency and iron deficiency anemia. This study suggested that congenital anemias such as hereditary spherocytosis or thalassaemia could be observed as coexisting hematological diseases in young patients with inborn errors of metabolism (7).

An infant with propionic acidemia and reversible pancytopenia has been reported in whom light and electron bone marrow microscopy revealed severely disturbed cellular morphology with trilineage dysmyelopoiesis, hemophagocytosis and abundant multinucleated histiocytes. Evaluation of the infant's hematological abnormalities suggests that inhibition of bone marrow proliferation and maturation and shortened red blood cell survival were responsible for her pancytopenia. The studies performed in vitro suspect the role of propionic acid in this hematopoietic dysfunction (8). Severe neutropenia is also reported in an infant with methyl malonic academia (9). Also, three children with disorders of propionate metabolism have been presented, ne with methylmalonic acidemia and two with propionic academia who developed secondary HLH during their metabolic attacks (10).

In patients with IVA, hematological problems are frequently reported in early infancy and during acidotic episodes; hence cytopenia is not commonly encountered in later childhood (11). Our patient was a three-year-old boy whose diagnosis of IVA was confirmed at this age. Inborn errors of metabolism specifically late onset form of IVA should be considered in differential diagnosis of any patient with varying degrees of cytopenia and metabolic acidosis after the neonatal period.

Patient Consent: Written informed consent was obtained from the patients' parents for publication of this case report.

Conflict of Interest: None declared.

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