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Case Report

# Pancytopenia Revealing Phenylketonuria: Coincidence or First Case Report

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ABSTRACT

Pancytopenia in childhood can be caused by a variety of underlying diseases including hematological and non-hematological entities. Phenylketonuria (PKU) is an inborn error of phenylalanine metabolism. No association between PKU and pancytopenia has ever been reported. We report the first case of PKU revealed by a pancytopenia at presentation. The patient was an infant girl born to healthy non-consanguineous parents with unremarkable family history. A hereditary metabolic disease workup was performed due to the presence of unexplained hematological features and a global developmental delay. Plasma aminoacid profile by thin-layer chromatography showed elevation of phenylalanine and urine organic acid chromatography showed accumulation of metabolites of phenylalanine; whereas, methylmalonic acid or other abnormal organic acids were not found. This is the first case of untreated PKU associated with pancytopenia who improved with low-phenylalanine diet.

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## Introduction

Pancytopenia in childhood can be caused by a variety of underlying diseases including hematological and non-hematological entities. These diseases may be congenital or acquired.[1] Among congenital causes, inborn errors of metabolism such as organic acidurias, lysinuric protein intolerance, inborn errors of cobalamin or folate metabolism, lysosomal storage disease (e.g. Gaucher disease) and respiratory chain disorders may present with pancytopenia. It may be transient during acute episodes or persistent.[2] Phenylketonuria (PKU) is an inborn error of phenylalanine metabolism.[3] No association between PKU and pancytopenia has ever been reported. We report the first case of PKU revealed by a pancytopenia at presentation.

## Case Report

The patient was an infant girl born to healthy non-consanguineous parents with unremarkable family history. The pregnancy and the birth were uneventful. A psychomotor delay was noticed at 3 months as she was not able to lift her head. Thereafter, all her milestones were delayed (she could support her head at the age of 7 months, started to babble at the age of 9 months and sat without help at 14 months old). She was investigated for isolated pallor since 9 months old. The complete blood count (CBC) showed a normochromic normocytic anemia (Hemoglobin: 8.3g/dL, hematocrit: 24.3%, MCV: 75, reticulocyte count: 0.45%). White blood cell and platelet counts were normal (respectively 7.7 × $10^9$/l and 162 × $10^9$/l). Iron and folic acid supplements were

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prescribed empirically as blood concentrations were not measured for these micronutrients at that time. During the following months, hematological parameters worsened with a hemoglobin concentration reaching to 3.1 g/dL. Progressive neutropenia and thrombocytopenia developed with a minimum count of neutrophils and platelets, respectively at $0.200 \times 10^9$/l and $17 \times 10^9$/l. Etiological workup of pancytopenia included a bone marrow aspiration which showed very rare megakaryocytes with decreased cellularity in granulocytes, erythroblasts and lymphocytes. Bone marrow biopsy showed diffuse and dense myelofibrosis associated with lymphoid infiltrates. Immmunophenotyping showed cells positive for CD20 and negative for CD3, TdT, CD34 and MPO. Serum ferritin concentration (after iron supplement) was normal (319 µg/l). Blood urea nitrogen and creatinine concentrations were normal. Blood biochemistry laboratory tests were within normal range. Vitamin B12 had not been measured since bone marrow findings were not suggestive of vitamin B12 deficiency. Serology of human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus and parvovirus B19 were negative. The chromosomal breakage analysis did not show signs of chromosomal instability so Fanconi anemia was excluded. Flow cytometry showed no features of paroxysmal nocturnal hemoglobinuria. BCR-ABL reverse transcriptase polymerase chain reaction was negative, so chronic myeloid leukemia was excluded. The JAK2 V617F mutation, associated with some types of myeloproliferative disorders was not found to be positive in this patient. The patient required several blood transfusions. A hereditary metabolic disease workup was performed due to the presence of unexplained hematological features and a global developmental delay. Plasma aminoacid profile by thin-layer chromatography showed elevation of phenylalanine and urine organic acid chromatography showed accumulation of metabolites of phenylalanine; whereas, methylmalonic acid or other abnormal organic acids were not found. The diagnosis of PKU was confirmed at the age of 17 months by determination of a high plasma phenylalanine level up to 1500 µM (normal up to 180 µM). She was referred to the inherited metabolic diseases reference center. On examination, she was pale, eutrophic with light skin and hair, contrasting with her mother's phenotype. She had mild truncal hypotonia with exaggerated tendon reflexes and microcephaly. She had autistic behavior with stereotypies. Her electroencephalogram showed abnormal recordings without clinical seizures. Brain stem auditory and visual evoked potentials and brain magnetic resonance imaging were normal. A Phenylalanine restricted diet was initiated. She received 220 mg of phenylalanine and 52 grams of phenylalanine free amino-acid formula per day. Phenylalanine levels normalized within one week of the provided diet. During the first month of treatment, she needed packed cells transfusions twice for severe anemia and then a progressive improvement in hemoglobin, white blood cell and platelet counts was noticed. CBC completely normalized within 4 months of treatment. When she was 30 months old, she was able to walk by herself and to say few syllables. She still has autistic traits with self-aggressiveness and stereotypies. All blood cells are within normal ranges and she does not need any further transfusions. Oral consent was obtained from parents.

## Discussion

Phenylketonuria (PKU) is an autosomal recessive inborn error of phenylalanine metabolism caused by mutations in the phenylalanine hydroxylase gene.[3] It results in accumulation of phenylalanine and its metabolites. In many countries, there is a systematic neonatal screening for PKU. Children treated early within the first weeks of life have normal intellectual development.[4] In the absence of neonatal screening, untreated PKU is associated with an abnormal phenotype including growth failure, light skin and hair, microcephaly, mousy odor, global developmental delay and seizures.[5] For the majority of PKU patients, the treatment is based on phenylalanine restricted diet. This diet is composed of a calculated amount of low-protein foods associated to phenylalanine free amino-acid formula supplemented with vitamins, minerals and trace elements.[6] Low phenylalanine diet can lead to several hematological complications. Iron deficiency anemia, megaloblastic anemia and pancytopenia caused by folic acid or vitamin B12 deficiency have previously been reported.[7] A two-year-old boy is reported that was diagnosed with classical phenylketonuria because of psychomotor retardation. He later developed an acute myeloblastic leukemia at the age of nine year old.[8]

Our case is the first case of phenylketonuria reported with pancytopenia that improved with restricted phenylalanine diet. In our patient, all common causes of pancytopenia were excluded; so that taking into account that the pancytopenia normalized after diet restriction in phenylalanine, we can presume that pancytopenia in this case was due to PKU and increased phenylalanine levels.

Two hypotheses could be raised to explain this uncommon association. The first one is that pancytopenia is the result of vitamin deficiency that was corrected by the phenylalanine-restricted diet. Vitamins had not been measured initially. However, our patient's history, the absence of methylmalonic acid in the urine (which is a common finding in vitamin B12 deficiencies)[9] and bone marrow morphology were against the diagnosis of vitamin B12 deficiency. Iron and folic acid supplements had no effect on hematologic parameters before the initiation of the diet. The phenylalanine free amino-acid formula contains very low amounts of cobalamin and folates (1.9 µg and 155 µg per 100 g of cobalamin and folate, respectively) (comidamed.de/downloads/en/PKU_Bf_e.pdf). Our patient received 1µg of cobalamin and 80 µg of folate per day. These doses are much lower than the therapeutic doses.[9] So, the hypothesis of vitamin deficiency seems to be unlikely. The only issue for this problem is to discontinue phenylalanine free amino-acid formula and to monitor the hematological parameters to search for the recurrence of the abnormalities. This is not possible ethically because this would lead to nutritional deficiency and poor metabolic control with the risk of

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more neurological damage.

The second hypothesis suggests a direct or indirect effect of hyperphenylalaninemia on hematopoiesis like in other inborn errors of metabolism such as organic acidurias, lysinuric protein intolerance or Gaucher disease. Gol'dberg ED et al. studied the regulatory effects of leucine-enkephalin (LE) on bone marrow hematopoiesis.[10] LE is an endogenous opioid neuropeptide with the amino acid sequence of Tyr-Gly-Gly-Phe-Leu that is found naturally in the brain of many animals, including humans. The enkephalins play an important role in many physiological functions including pain perception with morphine-like activity and response to stress.[11] In mice, immobilization stress leads to a bone marrow hyperplasia. Gol'dberg ED et al. showed that injection of LE, D-Phenylalanine or dalargin (synthetic LE) into immobilized mice inhibits this effect and causes suppression of hematopoiesis.[10] He also showed that activation of hematopoiesis was not registered in immobilized mice receiving LE in contrast to the control animals.[12] Other authors also demonstrated that the (4-Carboxamido) phenylalanine is the first example of an amino acid that acts as a surrogate for tyrosine in opioid peptide ligands.[13, 14] These two findings suggest that in phenylketonuria, hyperphenylalaninemia may have a LE-like effect on bone marrow causing suppression of hematopoiesis and may lead to pancytopenia.

## Conclusion

This is the first case of untreated PKU associated with pancytopenia who improved with low-phenylalanine diet. Underlying pathogenic mechanisms are not clear, but PKU should be kept in mind among inborn errors of metabolism potentially associated with hematological abnormalities. In addition to being a part of the regular monitoring of nutritional status in treated PKU, complete blood count should be included in the initial evaluation and follow up of every newly diagnosed patient. Furthermore, when unexplained pancytopenia is found, PKU should be considered in areas where neonatal screening is not implemented, especially when associated with neurologic or developmental abnormalities.

**Conflict of Interest:** None declared.

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