

Homocystinuria: A Rare Cause of Megaloblastic Anemia

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We present an eight-year-old boy who initially presented to us with megaloblastic anemia and subsequently developed dislocation of lens. The child had a positive sodium nitroprusside test and homocystinemia. He was diagnosed to have homo cystinuria type I. His anemia improved on oral pyridoxine and folic acid therapy. Homocystinuria should be remembered as a cause of megaloblastic anemia.

Key words: Homocystinuria, Megaloblastic anemia, Pyridoxine.

Homocystinuria is an inborn error of aminoacid metabolism in which homocystine, the disulphide of homocysteine, is excreted in the urine as a consequence of elevated homocysteine levels in the blood(1). Homocystinuria type I, due to deficiency of the enzyme cystathionine synthase, is the most common inborn error of methionine metabolism. It is characterized by mental retardation, lens dislocation, skeletal abnormalities and thrombotic vascular disease. Homocystinuria may also be due to defects in methyl cobalamin formation, *i.e.*, homo-

cystinuria type II, characterized by the triad of megaloblastic anemia, homo-cystinuria and hypomethioninemia. Deficiency of the enzyme methyltetra-hydrofolate reductase, results in homo cystinuria type III, which is characterized by homocystinuria and homocystinemia with low or normal blood methionine levels(2).

We encountered a patient with macrocytosis with bicytopenia and megaloblastic changes in the marrow, treated with folate and vitamin B₁₂ at this hospital. After the initial improvement in anemia, the patient reported back after two years with pallor and pain in his right eye when we made a diagnosis of homocystinuria and instituted specific treatment.

Case Report

An 8-year-old boy, born of non-consanguineous marriage, first presented with pallor to the out-patient department of this hospital. The child had a history of progressively increasing pallor for the past two years and of receiving one blood transfusion at the age of 6 year. On examination, the child was pale; there was no pedal edema, jaundice, petechiae, ecchymosis, hepatosplenomegaly, lymphadenopathy and sternal tenderness. Investigations showed hemoglobin level of 7.15 g/dL, total leukocyte count 5700 cells/mm³ and a normal differential count, platelet count 80,000/mm³ and reticulocyte count 1.8%. Peripheral smear revealed normochromic RBCs with few macrocytes and reduced platelets. The mean corpuscular volume was 128 fL, mean corpuscular hemoglobin was 37 pg and the mean corpuscular hemoglobin concentration was 29 g/dL. Bone marrow examination showed megaloblastic changes. The patient was started on treatment for megaloblastic anemia with 5 mg of folic acid and 100 µg of vitamin B₁₂ per

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day orally. After one month of treatment the hemoglobin improved to 10.4 g/dL and mean corpuscular volume reduced to 98 fL while the reticulocyte count increased to 4%.

After an initial improvement in anemia the patient was lost to follow-up. After two years the patient again came with pallor, and redness and pain in his right eye. On examination the intraocular pressure of his right eye was increased and bilateral inferonasal subluxation of lens was found. The right lens showed cataract and atrophic patches on the iris while the left lens was clear. The blood pressure was within normal limits.

The hemoglobin was 4.5 g/dL, total leukocyte count was 7500 cells/mm³ and the platelet count was 69000/mm³. The mean corpuscular volume was 112 fL and the mean corpuscular hemoglobin was 36.9 pg. Peripheral smear showed anisopoikilocytosis with macrocytes, ovalocytes, tear drop cells, polychromatic cells with coarse basophilic stippling, cabot rings and few microcytic hypochromic cells. Sodium nitroprusside test in urine was positive. The serum homocysteine level was 72.4 μ mol/L (normal range 5-15 μ mol/L) and vitamin B12 was 364 pg/mL (normal range 200-800 pg/mL). Stool examination for malabsorption for fat and reducing substance was negative; urinalysis was also normal. Doppler studies were normal. There was no evidence of osteoporosis in the radiographs of long bones of the patient. Qualitative estimation of fasting serum and urinary amino acids, using paper chromatography technique, showed raised fasting urinary methionine and homocysteine level and raised fasting plasma methionine level. On the basis of these investigations the patient was diagnosed as homocystinuria type I and started on oral pyridoxine (200 mg/day) and oral folic acid (5 mg/day). The intelligence quotient was 61-65 on Malin's intelligence scale. The

response to treatment was further assessed by a repeat plasma and urinary amino-acidogram(3,4). There was a disappearance of fasting plasma methionine and urinary homocysteine and methionine after 8 weeks of treatment. After 12 weeks of treatment, hemoglobin level was 13.3 g/dL, mean corpuscular volume was 84.7 fL, mean corpuscular hemoglobin was 27.8 pg and mean corpuscular hemoglobin concentration was 32.8 g/dL.

Discussion

Methionine is normally activated and converted to homocysteine. Homocysteine is further converted to either cysteine or methionine. The conversion of homocysteine to cysteine requires pyridoxal phosphate as a coenzyme while the methylation of homocysteine to methionine requires N5-methyltetrahydrofolate as methyl donor as well as methyl-B₁₂ as coenzyme(2,3). Normally homocysteine is an intracellular intermediate and is not detectable in plasma or urine. However, when the reconversion pathway of homocysteine to methionine or to cysteine is blocked, it accumulates extracellularly resulting in homocystinuria(3).

Classically megaloblastic anemia has been known to be associated with homocystinuria type II(2). In homocystinuria type II there is a deficiency of methyl B₁₂ as a result of which DNA synthesis is impaired due to interference with folate metabolism by trapping folate as methyltetrahydrofolate(1). Not many cases of megaloblastic anemia have been seen with homocystinuria type I(1). The pathogenesis implicated for megaloblastic anemia seen in homocystinuria type I is the development of folate deficiency due to the excessive consumption of N5-methyltetrahydrofolate in the methylation of homocysteine to form methionine(1,3). Thrombocytopenia seen in

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our patient can be attributed to folate deficiency which improved subsequently on treatment with folate(4).

The megaloblastic anemia seen in homocystinuria type II responds to treatment with vitamin B₁₂. However, treatment in homocystinuria type I constitutes administration of pyridoxine. Pyridoxine acts as a coenzyme for the enzyme cystathionine synthase and its administration results in greater binding of enzyme with substrate by simple mass action(5,6). However, due to associated folate deficiency, the response to pyridoxine may not be seen unless folate is also given concurrently. It has been observed that serum folate levels may fall further when homocystinurics are treated with pyridoxine due to increased remethylation of homocysteine to methionine(3,6).

We conclude that homocystinuria must be remembered as a rare but treatable cause of megaloblastic anemia. All patients with homocystinuria treated with pyridoxine should receive folate supplementation. The treatment of homocystinuria assumes greater significance because institution of specific treatment can prevent progression of this disease and associated complications.

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