Megaloblastic Anemia—A Rare Cause

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Abstract A 2-year-old boy presented with non-responsive megaloblastic anemia, growth failure and developmental delay. Blood levels of B12, folic acid and iron were normal. Tandem mass spectroscopy for common inborn errors of metabolism did not reveal any abnormality. There was an increased excretion of orotic acid in urine. The authors report this as a rare cause of megaloblastic anemia.

Keywords Megaloblastic anemia · Orotic aciduria · Child

Introduction

Over the years incidence of megaloblastic anemia seems to be increasing. In developing countries, in most instances it is due to vitamin B12 or folic acid deficiency [1]. Most of the children respond to vitamin B12 or folic acid supplementation [1]. Pernicious anemia due to intrinsic factor deficiency, malabsorption resulting in folate deficiency (celiac disease) and certain inborn errors of metabolism e.g. methylmalonic aciduria (B12 deficiency) and methyl tetrahydrofolate reductase deficiency (folic) account for minority of cases [1]. Thiamine responsive megaloblastic anemia, associated with sensorineural deafness and diabetes mellitus has been reported [2]. Disorder of pyrimidine metabolism, as a cause of megaloblastic anemia, is even rarer with only a few reported cases [3-5]. The authors report a rare case of megaloblastic anemia, due to orotic aciduria, a disorder of pyrimidine metabolism.

Case Report

Anemia in a boy was diagnosed as megaloblastic anemia at 6 months of age. It was assumed to be nutritional in origin. He was treated with B12 and folic acid supplementation without measuring the levels, as these deficiencies are cause in majority of cases. He received blood transfusion at 7 months and 14 months. He was receiving iron therapy for 7 months. At 2 years of age, he presented with severe anemia and congestive cardiac failure. There was no history of persistent diarrhea, dysentery, pica, fever or any chronic illness. His diet was adequate in calories and proteins. There was no consanguinity. Antenatal or post natal history was not suggestive of inborn errors of metabolism. Spleen was palpable 1 cm below costal margin. His weight was 9.2 kg (expected 12.2 kg) and height was 73 cm (expected 87 cm), head circumference was 43.3 cm (<3rd centile). All developmental milestones were delayed. Child had hypopigmented sparse hair, strabismus was absent. Hearing was normal.

Investigations at present admission revealed hemoglobin of 2.4 gm/dl(0.372 mmol/L), TLC $3 \times 10^9$ /L, DLC (Lymphocytes 62, Neutrophils 34, Eosinophil 2, Basophil 1, Monocyte 1) platelets $351 \times 10^9$ /L, RBC count $0.072 \times 10^{12}$/L and MCV of 98 fl, MCH 30.6 pg/ml (0.47 fmol/cell), MCHC 32.2(4.99 mmol Hb/LRBC). Reticulocyte count was 1.5%. B12 and folic acid levels were 1254 pg/ml (Normal 200–900 pg/ml) and >20 ng/ml (normal 5–20 ng/ml) respectively. Serum iron level was 64 μg/dL (Normal 22–184 μg/dL) and ferritin level was 32 μg/L. Blood sugar was 101 mg/dl. Arterial blood gases were normal. Hemoglobin electrophoresis did not reveal any abnormality. Blood urea was 19 mg/dl and creatinine 0.7 mg/dl. Ammonia and lactate
levels were normal. The peripheral blood smear revealed normocytic and macrocytic RBCs with relative lymphocytosis. Bone marrow examination was suggestive of megaloblastic anemia. Urinary excretion of orotic acid level was increased to 49.6 μmol/L (normal <5 μmol/L); urine aminoacidogram was normal. Tandem mass spectrometry to rule out other inborn errors of metabolism methylmelanonic academia, propionic academia, common fatty acid oxidation defects, arginemia and organic acid defects did not reveal any abnormality. Serum homocysteine level was 6.2 μmol/L, which was in the normal range. Urinary methylnalonic acid was 7 mg/day by liquid chromatography. MRI brain revealed mild cerebral atrophy. There was no skeletal abnormality. Megaloblastic anemia with normal B12 and folic acid level with increased excretion of orotic acid in urine was suggestive of hereditary orotic aciduria. Enzymatic estimation facilities were not available. Child was advised a diet rich in uridine (sugar cane juice and tomatoes) as commercial uridine was not available. With therapy, fall in hemoglobin level was just (1.2 gm/dl over 4 months) but there is no significant change in his developmental status.

Discussion

Oroticaciduria is a rare autosomal recessive disorder characterized by growth failure, developmental retardation, megaloblastic anemia, and increased urinary excretion of orotic acid [6]. The enzymatic defect involves deficiencies in uridine monophosphate synthetase, a multifunctional enzyme in normal pyrimidine synthetic pathway, which contains both orotate phosphoribosyltransferase(OPRT) and orotidine -5′-monophosphatase decarboxylase (ODC) activity. These enzymes have been shown deficient in erythrocytes, leukocytes, fibroblasts, and saliva of affected individuals [6, 7]. The enzyme orotate phosphoribosyltransferase (OPRT) first converts orotic acid to orotidine monophosphate which is then decarboxylated by the enzyme orotidine-5′-monophosphate decarboxylase to uridine 5 monophosphate. Thus, deficient activity of the enzymes results in excessive accumulation of orotic acid in the body [6–8]. These enzyme deficiencies affect the normal DNA synthesis and clinically child presents with macrocytic hypochromic anemia refractory to the iron, folic acid, or B12 therapy. Child usually presents in first year of life. Other features associated with hereditary orotic aciduria are leucopenia, failure to thrive, developmental delay, sparse hair, crystalluria, strabismus, splenomegaly and urinary obstruction. Although orotic acid is an important precursor in the synthesis of pyrimidines, only minute amounts are founds in normal blood and urine [6].

In 1959, Huguley et al. [4] first described hereditary orotic aciduria in a male child who presented with megaloblastic anemia since the age of 9 months, unresponsive to B12 or folic acid therapy. In 1968, Rogers et al. [3] described an infant who developed anemia since 2 months of age. Girot et al. in 1983 [5] reported two more cases of hereditary orotic aciduria and concluded that immunodeficiency is a integral part of orotic aciduria which was later questioned by Becroft et al. [8]. Imaeda M in 1998 [9] reported orotic aciduria in a case of cerebral palsy with mental retardation where both the mother and the child were heterozygotes and concluded that the insufficient pyrimidine nucleoside supply in the neonatal period may be the cause of neurological symptoms.

The present child developed symptoms of anemia in first year of life with associated developmental delay, growth failure and hypo pigmented sparse hair. He was not receiving any drugs known to cause megaloblastic anemia and bone marrow and peripheral smear examination ruled out any leukemic condition. Megaloblastic anaemia in absence of B12 or folic acid deficiency and increased urinary orotic acid excretion was consistent with the probable diagnosis of hereditary orotic aciduria. Crystalluria was absent. Confirmation of the diagnosis needs assay of the enzymes in patient’s erythrocytes, which was not carried out due to lack of facilities.

Treatment of hereditary orotic aciduria needs lifelong administration of uridine in doses of 50–300 mg/kg/day [9]. Long term prognosis of the uncomplicated case is good. Replacement therapy with uridine usually leads to a clinical and hematological remission and reduction in the urinary excretion of orotic acid.

Anemia is common in tropical countries as India. Iron deficiency is the most common cause for microcytic anemia. Among the causes of megaloblastic anemia B12 deficiency is more common and folic acid deficiency is also found, especially in series from north India [1, 10]. Rare causes of macrocytic anemia should be considered in cases not responding to initial supplementation of iron, folic acid or B12, orotic aciduria being one of them.

Contributions SKD, AA, HG, diagnosed and managed the case. SKD and HG searched literature and prepared the manuscript. AA critically reviewed the manuscript and will act as guarantor of the case.

Conflict of Interest None.

Role of Funding Source None.

References