CASE REPORT

Congenital dyserythropoietic anemia type II – a case report of two siblings in a family

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Abstract Two children out of three siblings of a family presented with tiredness, fatigue, and breathlessness for more than 6 months. Examination of peripheral blood smear, bone marrow aspirate, and a positive acidified serum test (HEMPAS) revealed these children to be a case of congenital dyserythropoietic anemia type II. This case is reported because of its rarity.

Keywords Congenital dyserythropoietic anemia type II(CDA-II) · Bone marrow aspirate

Introduction

The congenital dyserythropoietic anemias (CDA) are a group of genetic disorders characterized by ineffective erythropoiesis and dyserythropoiesis [1].

Congenital dyserythropoietic anemia type II (CDA-II) is an autosomal recessive disease that represents the most common form of CDA [2]. The etiology is unknown for all the forms [3].

It comprises an anemia of variable severity, jaundice and hepatosplenomegaly. A diagnosis of CDA-II is generally considered after other chronic hemolytic anemias have been ruled out [4]. Erythroid hyperplasia with binuclearity or multinuclearity involving late erythroblasts in the bone marrow is a key feature of the diagnosis. BM examination remains the gold standard for diagnosis [5]. The pathognomonic findings in CDA II are that the patient's RBCs are lysed by acidified serum. The combination of erythroblast multinuclearity and the sensitivity of circulating RBC to lysis by acidified normal serum is the reason that type II CDA is known by the acronym HEMPAS (hereditary erythroblastic multinuclearity with a positive acidified serum test) [6]

Case 1

A 5-year-old girl was admitted in the pediatric ward of the Regional Institute of Medical Sciences(RIMS), Imphal, Manipur, with the chief complaints of intermittent episodes of tiredness, fatigue, and breathlessness for the last 6 months. There was no history of fever, cough, chest pain, or jaundice. She had been treated with six blood transfusions as a case of Beta Thalassemia major in another local hospital and had attended our OPD for blood transfusion.

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There was no history of recurrent respiratory infections or diarrhoeas. Her birth, developmental, and dietary history were within normal limits. She was also fully immunized for age. There was no history of consanguinity between her parents or her grandparents.

On examination, she was afebrile, co-operative, grossly anemic and had a heart rate of 104/min, blood pressure of 90/60 mm Hg., and respiratory rate of 32/min. There was no jaundice, clubbing, cyanosis, or significant lymphadenopathy. However mild frontal and bi-parietal bossing with malar prominence was noted. She measured a weight of 12 Kg and height of 95 cm, head circumference of 53.3 cm and mid-arm circumference of 13.8 cm.

Liver was palpable 6 cm below the right costal margin with a span of 11 cm. Spleen was palpable 6 cm below the left costal margin with splenic notch also appreciable. The gall bladder was not palpable. Cardiovascular examination revealed a normal sized heart with normal S1 and S2 and a grade II ejection systolic murmur. Rest of the systemic examination was within normal limits.

Investigation reports

Complete blood count

Hb-5.4gm/dl, TLC-7000/cu.mm, DLC:P49%, L45%, M3%, E3%, ESR - 80 mm/1st hour, Platelet count - 2.5 lacs/cu.mm, Reticulocyte count-1.2%. RBC morphology was predominantly normocytic, normochromic with a few macrocytes.

Bone marrow examination

Hypercellular marrow with erythroid hyperplasia; predominantly dyserythropoietic maturation; normoblasts with a mixture of binucleate, multinucleate, multilobate and megaloblastoid erythroblasts with occasional pseudo inter-nuclear bridging and giantoblasts were also noted. M:E ratio was 1.5:1. The granulocytopoiesis and megakaryopoiesis were within normal limits.

Other tests

Ham's Test (Acidified Serum Test): Positive. Blood group: AB Positive; HbF - 0.9%; Direct Coomb's test : Negative. S. Ferritin - 110 mcg/L, S. Transferrin - 138mg/dL, S. TIBC - 480 mcg/dL. Liver Function Test (LFT): S. Bilirubin: Total - 0.9mg/dL, Indirect - 0.7mg/dL. SGOT - 45 U/L, SGPT - 40 U/L. S. Total Protein - 6.8g/dl, S. Albumin - 3.6g/dL. S. Alkaline Phosphatase-429U/L. Random blood sugar - 110mg/dL. Routine examination of urine: No abnormality detected (NAD). X-ray skull: NAD. Ultra-

sound scan of Abdomen showed hepatosplenomegaly. No gall bladder calculus was seen.

Case 2

A 10-year-old boy, elder brother of case 1, had similar complaints for the last 1 year. On October 2002, he was diagnosed as a case of iron deficiency anemia by some pediatricians and had received blood transfusion on two earlier occasions. Birth, developmental, and dietary history were within normal limits and he was also fully immunized for age. Family pedigree is same as in case 1.

On examination, he was afebrile, non-irritable, pale, and had mild pedal oedema and with a normal facies. There was no jaundice, clubbing, cyanosis, & lymphadenopathy. His pulse rate was 84/min, blood pressure 100/60 mmHg and respiratory rate 28/min. JVP was not elevated. He measured a weight of 21 kg, height of 124 cm, a head circumference of 52.8 cm, and a mid-arm circumference of 16.2 cm.

Cardiovascular examination revealed a normal sized heart with normal S1 & S2 and a grade II ejection systolic murmur. Abdominal examination revealed a firm liver 3 cm and spleen 2 cm below the costal margins. The gall bladder was not palpable and there was no evidence of free fluid. Rest of the systemic examination was within normal limits.

Investigation reports

Complete Blood Count

Hemoglobin of 5.5g/dl, TLC-6800/cu mm, DLC-P64%, L33%, E1%, M2%, ESR-40 mm/hr., Platelet count- 2.5 lac/cu mm, Reticulocyte count-2.2%. The Peripheral blood picture showed mild anisocytosis, predominantly normocytic, normochromic red cells with a few of macrocytes.

Bone marrow aspiration showed similar findings of case I. M:E ratio - 1.5:1.

Other tests

Hemoglobin F - 1.2%. Ham's test: positive. S. Ferritin - 80 mc.g/L, S. Transferrin - 120mg/dl, S. TIBC - 420mc.g/dl. Blood group: AB Positive. LFT: S. Total bilirubin - 1.2 mg/dl, Indirect bilirubin - 0.8 mg/dl, SGOT - 23U/L, SGPT - 30U/L, S. Total protein - 7.2g/dl, S. Albumin - 3.8g/dl. Random blood sugar - 88.0mg/dL.

Based on clinical and hematological data, a diagnosis of Congenital Dyserythropoietic Anemia type II were made in both children. The patients were treated symptomatically.

2 units each of blood transfusions were given in both cases. The cases were discharged on oral folate therapy and after appropriate counseling. The patients are being followed up till date.

Discussion

The classification of the congenital dyserythropoietic anemia was originally based on distinct differences in the morphology of the bone marrow erythroblasts [7]. Of the three types, type II is the commonest, identified by positive Ham's test and multinucleated erythroblasts. CDA Type I is characterized by binuclearity and inter-nuclear chromatin bridging of erythroblasts. CDA Type III is the rarest, identified by giant erythroblasts with upto 12 nuclei – the gigantoblasts [8].

Type II CDA (HEMPAS) has been reported in approximately 200 patients. Male-to-female ratio of occurrence is 0.9. The age at diagnosis ranges from infancy to adulthood with a median age of 14 years [9].

CDA I and II are autosomal recessive disorders and family members of affected children should ideally be screened [4]. The pedigree pattern seen in our cases; two affected of three siblings, one male and one female with phenotypically normal unaffected parental and grandparental ancestors, is suggestive of an autosomal recessive disorder.

The principal clinical features include hepatosplenomegaly, variable degrees of jaundice and hemolytic facies. These features are common to a number of hemolytic and dyserythropoietic anemias. A diagnosis of CDA II is considered only after exclusion of these [10].

Reticulocyte counts in CDA are typically normal to slightly increased [10]. In fact dyserythropoiesis is suspected when there is sub-optimal reticulocyte response for the degree of anemia, in the face of erythroid hyperplasia in the marrow. The erythrocytes of patients with CDA type II are lysed in the acidified serum lysis test (Ham's Test) but not the patient's serum. Consequently, CDA type-II is also described as hereditary multinuclearity with a positive acidified serum lysis test (HEMPAS) [11]. A positive Ham's test is also seen in paroxysmal nocturnal hemoglobinuria the difference being that here it is positive even in the patient's own serum.

Because of hemolytic symptoms, CDA II is not infrequently misdiagnosed as hereditary spherocytosis. Only bone marrow examination is the gold standard for diagnosis. Serum ferritin levels are high in congenital dyserythropoietic anemia. Secondary hemochromatosis is a known late complication of the illness [12]. In our cases, serum ferritin levels were normal but may increase with age. Chelation therapy forms an important part of management of patients with CDA [10].

Although splenomegaly is common, the recommendation regarding splenectomy is not uniform among hematologists. Splenectomy is sometimes of benefit because anemia improves and hemolysis decreases [5].

The message is that CDA should be considered in the differential diagnosis of any child presenting with anemia with hepatosplenomegaly with or without jaundice as these cases can easily be passed off as the more common anemias, especially the thalassemias, nutritional anemias etc.

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