A Rare Case of Hemoglobin E Hemoglobinopathy with Gaucher's Disease

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Abstract Hemoglobin (Hb) E mutation is common in north-east part of our country. The natural history of Hb E thalassemia is highly variable. The phenotype, for patients with similar mutations, can range from asymptomatic to transfusion dependent. Our patient presented at 2 years of age with failure to thrive and hepatosplenomegaly. Routine work up revealed microcytic, hypochromic red blood cells. Hb E homozygous was indicated on electrophoresis and hemoglobin HPLC. Evaluation of parents revealed Haemoglobin E trait in both. Therapeutic splenectomy revealed Gaucher-like cells. β -Glucocerebrosidase levels were low. Presence of Gaucher-like cells with normal β -glucocerebrosidase (pseudo-Gaucher cells) are known in leukemia, multiple myeloma, thalassemia and mycobacterial infections. Co-existence of Gaucher's disease with Hb E mutation is not reported to the best of our knowledge.

Keywords Hemoglobin E disease · Gaucher's disease · Gaucher cells · Pseudo-Gaucher cells

Introduction

Hemoglobin (Hb) E is one of the world's most common and important mutations [1]. It has been noted to be an important health problem in the Indian subcontinent and Southeast Asia. It is caused by a substitution of glutamic acid by lysine at codon 26 of the β -globin gene. This mutation also activates a cryptic mRNA splice site, which results in reduced synthesis of the β -E chain and leads to a

thalassemia phenotype. Hb E has a weakened α/β interface, leading to some instability during conditions of increased oxidant stress.

Gaucher's disease is an autosomal recessive glycolipid storage disorder, caused by mutations in the glucocerebrosidase gene *1q21*. This defect leads to reduced enzyme activity with accumulation of glucosylceramide in the macrophages of the reticuloendothelial system. Three clinical subtypes of Gaucher's disease have been described on the basis of the absence (type I) or presence (types II and III) of a neurological component. Type I is more common, and is especially prevalent, among Ashkenazi Jews (predicted prevalence is about 1/850) [2]. More than 200 mutations have been identified in the β -glucocerebrosidase gene, including point mutations, crossovers, and recombinations.

Case Details

The patient is a product of consanguineous marriage and both her parents are residents of north eastern India. The child presented with features of failure to thrive and abdominal distention when she was 2 years of age. On examination, hepatosplenomegaly was present. Her routine blood investigations revealed a low Hb and hematocrit. MCV and MCH were low, RDW was high. Peripheral blood smear revealed microcytic, hypochromic red blood cells with presence of target cells and tear drop cells. Her Hb electrophoresis showed 1.8 % Hb A, 5.6 % Hb F and 92.3 % Hb A₂. Hb electrophoresis was done for both parents and showed heterozygous Hb E trait. Her sibling's Hb E electrophoresis was normal. HPLC of the patient revealed 11.3 % HbF, 3 % Hb A and 82.2 % HbA₂+E. A diagnosis of Hb E homozygous disease was made.

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Due to massive hepatosplenomegaly, splenectomy was done for the patient when she was 5 years old. Spleen specimen weighed 900 g and measured $21 \times 13 \times 3$ cm. Cut section revealed a congested spleen. Histopathological examination (B/520/10) showed complete effacement of parenchyma by phagocytic cells having abundant granular, fibrillary fatty cytoplasm and eccentrically placed nuclei [Fig. 1]. PAS stain was positive in the histiocytes [Fig. 2]. ZN stain for AFB was negative. Storage disorder was suggested on histopathological examination of spleen. After an year, the patient again presented with complains of snoring and recurrent cough for an year and examination revealed adenoid hypertrophy. Adenotonsillectomy was done for the same. Her Hb was 8.9 g/dL, hematocrit 28.4, MCV-68.7fL, MCH-21.6 pg, MCHC-31.4, RDW-17.5. Bone marrow examination was done to rule out infiltration by histiocytic cells. Bone marrow biopsy (B/2661/11)

Fig. 1 HE stain-complete replacement of splenic parenchyma by Gaucher-like cells

Fig. 2 PAS stain-intense positivity in Gaucher-like cells

Fig. 3 HE stain-bone marrow section shows numerous Gaucher-like cells

revealed massive histiocytosis [Fig. 3] with grade III myelofibrosis with evidence of granulomas. β -Glucocerebrosidase levels were done at this time to rule out the possibility of Gaucher's disease and were found to be low in blood (1.30 nmol/hr/mg, normal- > 4 nmol/hr/mg). Value of the control run along with the test sample was 4.8 nmol/hr/mg. To confirm the accuracy of true deficiency for gaucher enzyme, test for GM1 was done which was found to be 90.23 nmol/hr/mg.

With the cumulation of the above findings, we hereby report a case of Gaucher's disease co-existing with homozygous Hb E disease

Discussion

Hb E trait is common in north-eastern part of our country. The natural history of Hb E thalassemia is highly variable. The phenotype, for patients with similar mutations, can range from asymptomatic to transfusion dependent.

Hemoglobin E trait has no clinical significance. Patients may have mild microcytosis without anaemia [3]. The picture may be confused with iron deficiency unless laboratory studies are completed. The red cell morphology may show targeting.

Hemoglobin EE individuals are asymptomatic with very mild anaemia and microcytosis [3]. The red cell morphology picture may be similar to other thalassemia traits or mild thalassemia intermedia conditions. Targeted and irregularly contracted cells are commonly seen. Occasionally, patients have splenomegaly.

It is important to distinguish Hb E disorders diagnostically because of this marked difference in clinical course.

DNA-based diagnosis of Hb E disorders is optimal and necessary before genetic counseling is undertaken [4].

Screening tests may suggest other mutations, unless one is familiar with the findings. In testing with alkaline Hb electrophoresis, Hb E migrates with C, O Arab, and A2. Diagnosis of concomitant β -thalassemia requires DNA testing.

The most serious Hb E syndrome is Hb E β -thalassemia. The compound heterozygote state of Hb E β -thalassemia results in a variable phenotype ranging from a complete lack of symptoms to transfusion dependency.

Our patient was diagnosed as a case of HbE-homozygous disease at an early age. Subsequently when the child underwent therapeutic splenectomy, histopathological examination revealed gaucher-like cells. Gaucher cells are typically large cells measuring 50–60 μm in diameter with a small eccentric nucleus and fibrillary cytoplasm.

The pseudo-Gaucher cells are similar in many ways to true Gaucher on light microscopic examination but certain distinguishing features exist. Gaucher cells show diffuse iron staining, whereas pseudo-Gaucher cells are generally negative.

Pseudo-gaucher cells occur due to increased cell turnover, thereby leading to a relative enzyme deficiency [5]. Gaucher-like or pseudo-Gaucher cells have been seen in a variety of conditions such as acute lymphoblastic leukemia, Hodgkin's disease, thalassemia, and multiple myeloma [6]. On electron microscopy, Gaucher cells contain tubular cytoplasmic inclusions, which are absent in pseudo-Gaucher cells that instead contain crystals. These are derived from increased load of leukocyte membrane derived glucosyl-ceramide presented to macrophages under conditions of high cell turnover [5]. Gaucher-like cells in bone marrow have also been reported in cases of atypical mycobacterial infection especially in immunocompromised

patients [7]. Therefore, stains for acid fast bacilli (AFB) were performed which were negative in our case.

The spleen as well as the bone marrow of this child revealed gaucher-like cells. Definite diagnosis of Gaucher's disease was made by measuring the β glucocerebrosidase activity in the presence of organomegaly, cytopenias and typical Gaucher cells.

This case report highlights the co-existence of gaucher disease and homozygous Hb E. Association of pseudo-Gaucher cells with thalassemia has been studied and many case reports been published in the past. However, such a case is unreported so far to the best of our knowledge.

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