Fanconi Anemia with Incidental Haemoglobin E Trait: The First Reported Case in Literature

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Abstract Fanconi anemia (FA), commonly inherited as an autosomal recessive trait, is the commonest cause of inherited bone marrow failure syndrome often accompanied by skeletal deformities, genitourinary abnormalities and an increased risk of malignancies especially acute myeloid leukemia. Haemoglobin E ($\beta^{26} \text{Glu} \rightarrow \text{Lys}$) is common haemoglobin variant in the north-eastern part of India and the northern part of West Bengal. Here, we report a case of FA with concomitant haemoglobin E-trait in a 5-year-old child who presented with weakness, epistaxis, malaena and intermittent fever. She had a hyper-pigmented patch over the nape of neck and polydactyly. Complete blood counts revealed pancytopenia. The bone marrow aspiration and trephine biopsy showed marrow hypoplasia. Chromosome analysis showed chromatid and chromosome breaks in 22 % cells suggestive of FA. The results were corroborated with MMC stress test. Thus, we present the first reported case of FA with haemoglobin E-trait.

Keywords Fanconi anemia · Haemoglobin E trait · Polydactyly

Introduction

Aplastic anemia, usually in association with one or more somatic abnormalities is the presenting feature of few inherited disorders. Among them, Fanconi anemia (FA) is the commonest with the occurrence rate one in 10,00,000 [1]. It was first described by Fanconi [2] in the year 1927 as an autosomal recessive disorder in which there is progressive bone marrow failure and an increased predisposition to malignancy, especially acute myeloid leukaemia. Most, but not all, affected individuals also have one or more somatic abnormalities including skin (café-au-lait spot), skeletal (absent thumbs, radial hypoplasia, scoliosis), genitourinary (under developed gonads, horse shoe kidneys), gastrointestinal, cardiac and neurological anomalies [3].

Haemoglobin E ($\beta^{26} \text{Glu} \rightarrow \text{Lys}$), is a common haemoglobin (Hb) variant in South-East Asia. It is an asymptomatic condition but its importance lies in the fact that it can combine with beta-thalassaemia trait to produce E- β thalassaemia.

After a meticulous search of all available published literature no case report of FA with Hb E trait was found. So here, we present possibly the first reported case of FA with concomitant Hb E trait.

Case Report

A 5-year old girl presented at paediatric emergency department with the complaints of epistaxis, melena and pain abdomen for the last 4 days. She complained of weakness and breathlessness on exertion for the last 2 years. No previous episodes of bleeding could be elicited. All her childhood milestones including birth weight were normal. She had previously received 4 units of blood transfusion the last transfusion being given 2 months back.

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The girl belonged to the Rajbanshi community, who are the original local inhabitants of the northern part of the state of West Bengal in India. On examination, the child had height and weight appropriate for her age and sex, severe pallor, mild icterus and purpuric spots all over the body. There was no organomegaly or lymphadenopathy. She had an extra thumb in each hand (polydactyly) and a hyper-pigmented patch (café au lait spot) over the nape of her neck (Fig. 1). The X-ray of the left fore-hand confirmed polydactyly (Fig. 2).

The complete blood counts (CBC) revealed a Hb percentage of 28 g/L, haematocrit of 0.10 L/L and RBC count of $0.97 \times 10^{12}/L$. The other parameters were mean corpuscular volume (MCV) of 95.9 fl, mean corpuscular haemoglobin (MCH) of 28.9 pg, MCH concentration (MCHC) of 301 g/L % and red cell distribution width (RDW) of 27.6 %. The WBC count was $3.7 \times 10^9/L$ and a platelet count of $80 \times 10^9/L$. The corrected reticulocyte count was 0.5 %. The peripheral blood film (PBF) revealed normocytic normochromic RBCs, few fragmented red cells, target cells and moderate anisocytosis. Based on the PBF findings, Hb variant study and bone marrow study was suggested. The bone marrow aspiration showed hypoplastic marrow which was then confirmed by trephine biopsy (15 % cellularity) (Fig. 3).

The anticoagulated blood was subjected to Hb variant study by high performance liquid chromatography (HPLC) using beta-thal short program. The HPLC (BIORAD Variant, beta-thal short program) revealed that the patient had Hb E-trait with Hb A₂+E of 27.8 % (Fig. 4).

Other investigations like X-ray of left fore-arm, chest X-ray, ultrasonography of whole abdomen and pelvic region, electrocardiogram (ECG), echo-cardiography were done and all reports came out to be normal. A provisional diagnosis of inherited bone marrow failure syndrome,

possibly FA with Hb E-trait was made. A chromosome analysis on bone marrow aspirate showed 46XX chromosome pattern. Chromatid and chromosome breaks were seen in 11 (22 %) cells with a total of 18 breaks. Few aneuploid cells were also noticed with inconsistent chromosome missing, e.g. 21, 20, 9 etc (Fig. 5).

A strong suggestion of FA was made which was confirmed by diepoxybutane-mitomycin C (DEB-MMC) stress test. A strong suggestion of FA was made which was confirmed by MMC stress test. The test was done on peripheral lymphocytes which showed about a 100-fold increase of chromosomal breaks and a 200-fold increase of radial figures compared to the cells of healthy controls at the highest concentration 80 ng/mL of MMC.

Thus, the child was diagnosed as a case of concomitant FA with Hb E trait. Parental study revealed that both parents were carriers of Hb E but no positive family history for bone marrow failure could be obtained. Unfortunately, the patient died 3-months following the diagnosis.

Discussion

The congenital or constitutional forms of bone marrow failure share the presence of defects in the hematopoietic stem cells. FA is the most frequent form of congenital bone marrow failure syndrome usually associated with a variety of skeletal abnormalities. At birth, the blood counts are usually normal and pancytopenia usually develops insidiously between the ages of 5 and 10 years with a mean age

Fig. 1 Photograph of the Rajbanshi girl with Fanconi anemia and Hb E-trait. Inset in upper left shows polydactyly (white arrows). Inset in lower right shows café au lait spot in the nape of neck (black arrow)

Fig. 2 X-rays of the hand showing polydactyly

Fig. 3 The microphotograph of the PBF showing pancytopenia with target cells (black arrow) and few fragmented RBCs. (Leishman stain, $\times 400$ magnification) inset in upper left shows hypocellular marrow in bone marrow aspiration which was confirmed by trephine biopsy (inset in lower right)

of 7 year but may develop in adolescence or even in adult life. [4] The Hb and platelet counts are usually first to fall and the granulocytopenia is usually late to appear. Eventually, a global the bone marrow failure develops. Bone marrow failure leading to fatal haemorrhage or infection is the main cause of the death in FA patients. The median survival time for FA patients is 30 years. [5]

FA is associated with an increased risk of leukaemia of acute myeloid type, particularly FAB types M4 (myelomonocytic) and M5 (monocytic) and other malignancies like hepatic tumours and squamous cell carcinoma of the vulva, oesophagus, head and neck. [6]

FA should be differentiated from other congenital causes of bone marrow failure syndrome like dyskeratosis congenita and Diamond-Blackfan anemia where there is no increased tendency of chromosomal breakage. Cells derived from individuals with other chromosomal breakage syndromes, such as Bloom syndrome or ataxia-telangiectasia, may also exhibit high rates of spontaneous chromosomal breakage; however, only FA cells exhibit increased chromosomal breakage and radial forms in response to DEB or MMC [7].

Haemoglobin E is a common in south-east Asia and north-eastern part of India. Hb E trait subjects may have normal blood counts and are clinically asymptomatic. They may also have an increased red cell count with reduced MCV and mean cell haemoglobin (MCH), with or without mild anemia. Haemoglobin does not usually fall much below 120 g/L. The MCHC is normal or occasionally increased. The blood film may be normal or may show hypochromia, microcytosis, target cells, irregularly contracted cells, basophilic stippling or any combination of these features [8]. On HPLC, Hb E co-elutes with Hb A₂.

Fig. 4 Chromatogram showing HB A₂/E level of 27.8 % (HPLC; BIORAD, beta thal short program)

However, it appears that co-occurrence of this rare inherited syndrome with a common innocuous hemoglobinopathy was a chance occurrence without any significant management implications for the former condition.

Another interesting aspect of this case is the absence of macrocytosis and the level of Hb F. Elevated HbF and red cell macrocytosis are common in FA. Their absence in our patient may be due to the concomitant hemoglobinopathy. However, definitive attribution is difficult as the association is previously undocumented.

Our case was that of a 5-year old child who was suffering from pancytopenia with bleeding manifestations owing to reduced platelet count. The peripheral blood picture of target cells and fragmented RBCs prompted investigations of hemoglobinopathies which revealed Hb E trait. The somatic abnormalities (polydactyly, hyper pigmented patch) provided clue to the possible cause of congenital bone marrow failure syndrome which led to the diagnosis of FA.

FA with haemoglobinopathies has rarely been reported. There is only one previously reported case of concomitant FA with sickle cell trait in a child [9]. However, even after diligent search we could not find any other reported case of FA with a hemoglobinopathy in medical literature.

Hence, here we report the first case of FA in a patient having Hb E-trait who presented with bleeding manifestations.

Fig. 5 Chromosomal analysis with GTG banding show chromatid and chromosome breaks (black arrows)

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