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CASE REPORT

Fanconi anemia

F Ahammad[1], HS Rupa[2], AKMM Rashid[3], CH Rasul[4]

Abstract

Fanconi Anemia (FA) is a rare potentially life threatening autosomal recessive disorder characterized by progressive pancytopenia, multiple congenital anomalies with multiple type of cancer risk. The presentation may be variable but typical presentation make the diagnosis easy. Diagnosis of FA can be confirmed by chromosome break study which is regarded as the gold standard diagnostic test for FA. Only one case report of FA had been published from Bangladesh till now. Here is the second variety of FA. If FA is confirmed then a set of preventive strategy can be applied. On the other hand misdiagnosis may lead to mismanagement which is not uncommon.

Introduction

Fanconi anemia (FA) was first described and named as a disease in 1927 by the Swiss pediatrician Guido Fanconi, 3 brothers with a specific combination of bone marrow failure and various physical abnormalities, short stature, hypogonadism and hyperpigmentation.[1] FA is classified into the chromosomal instability syndromes (Ataxia telangiectasia, Bloom syndrome and Werner syndrome) by its genetic pathological characteristics. Chromosomal instability syndromes are groups of disorders due to the defects in DNA repair, increased risk of cancer, and other phenotypic changes.[2,3] FA is also classified into another group of syndromes, inherited bone marrow failure syndromes by its hematologic abnormalities. Bone marrow failure syndromes are defined as the failure of the hematopoietic function of the bone marrow and they are: Amegakaryocytic thrombocytopenia, Diamond Blackfan anemia, Shwachman Diamond syndrome, thrombocytopenia with absent Radie.[4] Care should be taken not to confuse it with Fanconi's syndrome which is a kidney disease.

FA is found in all races and ethnic groups and the estimated incidence of FA is approximately 1 in 160,000-360,000 live births in the general population but it is much higher in some ethnic groups.[5] The carrier frequency of FA in the general population worldwide is at 1:300.5 The ratio of male to female of FA patients is close to 1:1.

FA is an autosomal recessive disorder presenting with congenital anomalies, very high frequency of bone marrow failure, hematologic malignancies, commonly acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), and non hematologic malignancies, commonly squamous cell carcinoma. The median age of clinical onset of anaemia is 8 years old. The most common anomaly in FA is hyperpigmentation as well as Cafe-au-lait spots (55%). Other common features are short stature (51%), growth failure, hypogonadism and genital changes (35%), microcephaly (30%), renal anomaly (20%).[6]

FA is caused by the mutations in FA genes coding for the production of proteins that contribute to protecting and repairing damaged DNA. FA is classified into 15 different complementation groups and they are scattered widely throughout the human genome on I I different chromosomes.

We are reporting this case to emphasize that proper diagnosis of FA could be helpful for the family by adopting appropriate supportive treatment and some preventive measures.

Case Report

Emdadul, 11 years old boy hailing from Moheshpur, Jheniadah got admitted on 06/09/2015 in Khulna Medical College Hospital with the complaints of deformed upper limbs since birth and gradual pale coloration of whole body for 4 years.

According to his father's statement he was born. by normal vaginal delivery at home at term and

1. Forrukh Ahammad MD, Asst. Professor, Dept. of pediatrics, Khulna Medical College & Hospital.
2. Habiba Sultana Rupa MBBS, Asst. Registrar, Dept. of pediatrics, KMCH
3. AKM Mamunur Rashid MD, Associate Professor, Dept. of pediatrics, KMC&H
4. Choudhury Habibur Rasul FCPS, Professor of pediatrics (Rtd), KMC&H

birth was uneventful. He was born with upper limb deformity. He was relatively well for 7 years. Then he developed intermittent low grade fever and became lethargic. He has no deafness, no history of convulsion, hematemesis, melena or bleeding from any site. But he had history of two times blood transfusion. He is the second issue of consanguineous parents. Other sibling is normal.

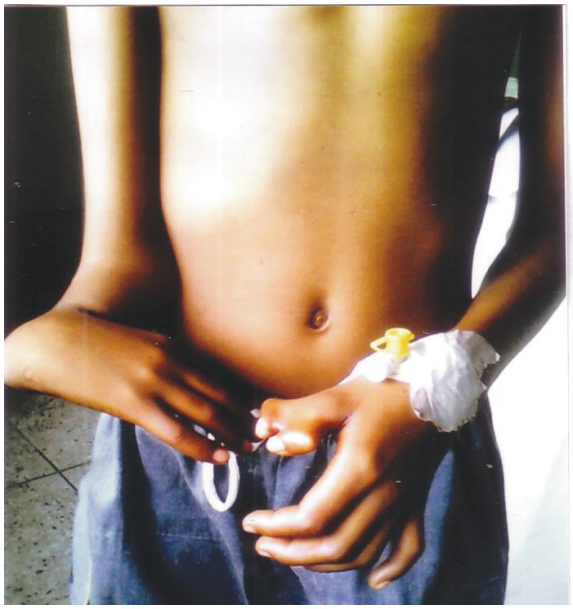

Fig. 1: Absent thumb and flexor deformity of right hand with bifid thumb of left hand

On Examination the patient was ill looking and severely pale. Jaundice, cyanosis, clubbing, edema and dehydration was absent. Lymph nodes not palpable. Bony tenderness absent. BP 90/60 mmHg, Resp. rate 24/min. OFC-45 cm which is below 3rd centile. Height 127.5 cm Ht for age Z score -2.6 SD. Wt-15 kg, BMI- 9.22. No cafe au lait spot. Deformed upper limb with absent thumb on right hand, small forearm, hand is turned inward.

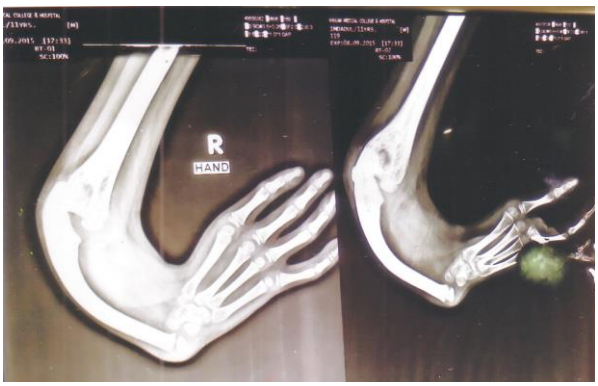

Fig. 2: X-ray of right hand and forearm showing absent thumb and radius

Left hand has bifid thumb (Fig 1). Liver, spleen not palpable, no cleft palate and no capillary hemangioma. Lower limbs were normal and there was no cardiac murmur and hearing impairment.

On investigation: CBC Hb-4 gm./dI, ESR-65mm in 1st hr, total WBC count- 3500/cmm, Platelet <50,000/cmm, PBF- Pancytopenia. S. creatinine 0.9 mg/dI. Bone marrow examination shows hypo cellular marrow. USG of whole abdomen revealed absent left Kidney. X Ray right hand and forearm showed absent radius and 1st metacarpal (Fig. 2). Haemoglobin electrophoresis could not be done for poor affordability.

The boy was managed by blood transfusion and antibiotic for infection. Androgen therapy was offered but patient's guardian refused for its cost and adverse effect. So we had tried low dose prednisolone and advised to follow up. Unfortunately patient came for only one follow up and then we missed the case.

Discussion

Diagnosis of FA sometimes may be difficult due to its variable presentation and involvement of multiple organ system. At presentation, patients may have: 1) typical physical anomalies. but normal hematologic findings; 2) normal physical features, but abnormal hematologic findings; or 3) physical anomalies and abnormal hematologic findings, the classic phenotype (39% of Cases).6 In our case both physical and hematological features were present. After an extensive search we have found only one case report on FA from Bangladesh. That case was a boy of 2 year 9 month of age with bilateral absent radii and thumb, absent left kidney and right testis and positive chromosome break test by Mytomycin C.7

Among the differential diagnosis thrombocytopenia absent radies (TAR) syndrome is considered first. Hall et al. set the current diagnostic criteria for TAR syndrome these include bilateral absence of the radii in the presence of both thumbs and a thrombocytopenia. In our case absent radius is unilateral and thumb was absent. The presence of the thumbs distinguishes TAR syndrome from other disorders featuring radial aplasia, which are usually associated with absent thumbs.[8] In Holt Oram syndrome (HOS), radial aplasia is associated with absence of the thumb and cardiac anomalies (ASD, VSD, Heart block), thrombocytopenia does not occur, and there is often a family history of heart and limb defects. HOS is an autosomal dominant disorder. Roberts syndrome is a multiple congenital anomaly syndrome consisting of pre and postnatal growth retardation, facial clefting, and renal and genital abnormalities. Limb defects may affect the upper or lower limbs or both. It is regarded as the

severe form of TAR syndrome.

Investigation of FA should be targeted for diagnosis and for involvement of organ system. Hematologic studies are complete blood count, peripheral blood film, bone marrow biopsy and reticulocyte count. The unique method called "chromosomal fiagility testing" using clastogenic agents, mitomycin C (MMC) and diepoxybutane (DEB) is described as the "Gold Standard" with the features of simple, reliable, reproducible and sensitive comparing with other testing methods in FA diagnosis.[9] This test was not done to this patient due to unavailability of the test in our institution and patient can't afford to do it in higher center. HbF level can be done which is increased.

Treatment of FA should be multidisciplinary approach and pediatric hemato-oncologist should play the pivotal role. Hematologic management can be given by blood transfusion, infection control by antibiotics, androgen therapy and stem cell transplant FA is significantly responsive to androgen therapy. Unfortunately the hematologic response is very short when this therapy is stopped thus showing androgen dependency. On the other hand androgen therapy has some side effects such as hirsutism and hepatic dysfunction. Nutritional management, hormone therapy and management of other organ involvement when required is important part of management. If FA is confirmed, a set of preventive strategy can be applied. These include carrier detection (parents and sibling), antenatal diagnosis (anomaly scan by ultrasonography, amniocentesis or chorionic villous sampling for chromosome break study) and family planning.

It is important to diagnose FA accurately so that appropriate investigation can be planned, relevant intervention can be given, and outcome can be assessed and counselled accordingly. With typical features, FA can be diagnosed with certainty, but with atypical presentation diagnosis of FA can be challenging. FA is a genetically and phenotypically heterogeneous disease and also because FA shares many clinical features with several group of diseases/syndromes. Early diagnosis and appropriate management is very important for Fanconi anemia.

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