Fanconi anemia: a rare aplastic anemia in a four year old boy-a case report and literature review

N Mahmud[1], AKMR Karim[2], SH Hasan[3], GMT Ali[4]

Abstract

Fanconi anemia is a rare autosomal recessive inherited bone marrow failure syndrome which can affect all races. It is characterized by congenital abnormalities, defective haemopoiesis and a high risk of developing acute myeloid leukaemia and certain solid tumours. Approximately 75% of the patient diagnosed between 3-14 years of age. The diagnosis is based on morphological abnormalities, hematologic abnormalities and genetic tests. We present here a case of a boy suffering from anemia with hyperpigmentation of skin, café-au-lait spot, growth failure, absent radius and thumb, characteristic facies, undescended testes and congenital heart disease. Pancytopenia, dysplastic marrow and multiple congenital anomalies may be a clue to diagnosis in a center which has no facility to do advanced tests.

Keywords: Fanconi anemia, aplastic.

J Cox Med coll 2017;3(2): 42-44

Introduction

FA (Fanconi anemia) is an autosomal recessive inherited bone marrow failure syndrome. Rarely it can be transmitted in X-linked recessive manner[1]. Overall incidence of FA throughout the globe is less, but it is the commonest among inherited pancytopenias[2]. It has been found in all ethnic groups. Its frequency has been estimated to be 1/350,000 births with a higher frequency in Ashkenazi Jews and Afrikaners in South Africa[3]. Approximately 75% of the patients are 3- 14 years of age at the time of diagnosis[2]. Ten percent of the cases may be diagnosed in the neonatal period[3]. The disease generally associated with multiple congenital anomalies and predisposition to malignancies along with hematological problems[4]. FA frequently terminates in myelodysplastic syndrome and/ or acute myeloid leukemia.1 At presentation, patients may have: 1) physical anomalies and abnormal hematologic findings, the classic phenotype (Majority of patients) 2) normal physical features, but abnormal hematologic findings(about one third of patients); or 3) typical physical anomalies, but normal hematologic findings(unknown percentage)[2]. FA cells are characterized by chromosomal hypersensitivity to cross linking agents and the resulting increase in chromosome breakage provides the basis for a diagnostic test[5]. Here we present a patient who had classical features of FA.

Case report

Four years old immunized boy of non consanguineous parents from rural area of Chittagong was presented with not growing well, progressive blackening of skin and deformity of upper limbs. Birth history was uneventful and no history of gross malfeeding. Milestones of development were age appropriate. On examination, he was pale, generalized skin pigmentation including palate with dental caries. Multiple café-au-lait spot present all over the body. He had Short forearm and thumb was absent in both upper limbs. His weight was 7 kilo(weight for age Z score -6.9SD), height was 79 centimeter (Height for age Z score -5.4 SD and weight for height Z score -4.9 SD), occipitofrontal circumference 42 cm (OFC for age Z score -5.3 SD). He had short stature, microcephaly, nanophthalmous and microcornea. On cardiac evaluation, apex was located in left 5th intercostals space lateral to mid clavicular line with continuous murmur, more prominent in left 2nd intercostals space suggestive of patent ductus arteriosus (PDA). His both scrotal sacs were empty. Complete blood count and peripheral blood film was carried out which revealed Hb%=9.2 gm/dl, Mean corpuscular volume (MCV)=86.8 fL, Mean corpuscular hemoglobin (MCH)=30.2 pg, Mean corpuscular hemoglobin concentration (MCHC)=34.8g/dL, TC

1. Prof. Nasiruddin Mahmud
Professor of Paediatics
Chittagong Medical College.

2. Prof. AKM Rezaul Karim
Professor of Paediatics
Chittagong Medical College.

3. Dr. Syeda Humaida Hasan
Consultant of Paediatics
Chittagong Medical College.

4. GM Tayeb Ali
MD 3rd Part Student
Chittagong Medical College.

Correspondence
Prof. Nasiruddin Mahmud
E-mail: mahmudcmc24@gmail.com

of WBC=6700/cu mm and platelet=40,000/cu mm. Bone marrow study revealed erythropoiesis, granulopoiesis and megakaryopoiesis were dysplastic and depressed. PDA was confirmed on

Figure-1:Short stature with hyperpigmentation

echocardiography. There was no renal abnormality on ultrasound. Both testes were found in inguinal canal. Imaging of upper limb showed absent radius and absent thumb. Clinical history, physical examination and hematological reports all were in

Figure-2: Café-au-lait spot on back

favour of fanconi anemia. Chromosomal breakage test in response to DEB (diepoxybutane) and MMC (mitomycin C) were not possible to do due to poor economic conditions of the parents. After diagnosis, along with other supportive measures, he was

Figure-3: Dental caries with gingivitis

treated with packed red cell and platelet transfusion. Androgen therapy was not available in the market and Allogenic hematopoietic stem cell transfusion (HSCT) was not affordable for the poor patient. At the time of diagnosis, he didn't have bleeding from any site which he developed in the course of time in the form of gum bleeding and subconjunctival hemorrhage. Now patient is on demand transfusion of blood components and low dose steroid therapy. The demand for transfusion is increasing day by day.

Discussion

Fanconi anemia was first described in 1927 by the Swiss paediatrician Guido Fanconi, who described a familial form of aplastic anaemia in three brothers [5]. According to International Fanconi Anemia Registry, more than 1,200 cases of FA have been reported[6]. FA belongs to chromosomal instability syndrome characterized by cellular hypersensitivity to interstrand DNA crosslinking agents, such as cisplatin, mitomycin C (MMC), diepoxybutane (DEB) and melphalan[7]. Clastogens also induce G2/M cell cycle arrest. In addition there is sensitivity to oxygen free radicals and to ionizing radiation[1]. The genes that have been found to be mutated in FA patients are called FANC. To date 16 distinct FANC genes (FANCA, FANCB, FANCC, FANCD1 (also known as BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ, FANCL, FANCM, FANCN, FANCO, FANCP, and FANCQ) have been reported. Among these, mutations in FANCA are the most frequent among FA patients worldwide and also among Indian patients[4,8]. Only FANCB mutations are inherited in an X-linked manner[9].

The most common anomaly is hyperpigmentation of the trunk, neck, and intertriginous areas, as well as café-au-lait spots and vitiligo, alone or in combination[3]. Half of the patients have short stature which is an integral feature of FA. In some patients, growth failure is aggravated by superimposed endocrinopathies either growth hormone deficiency or hypothyroidism[2,5,10]. Absence of radii and thumb defects are the most common skeletal abnormalities. Males may have an underdeveloped penis; undescended, atrophic, or absent testes; and hypospadias or phimosis. Many patients have a Fanconi "facies," including microcephaly, small eyes, epicanthal folds, and abnormal shape, size, or positioning of the ears. Approximately 10% of patients are cognitively delayed. Renal anomalies seen in 21% patient[1,2]. Less common abnormalities in FA include gastrointestinal defects such as atresia, imperforate anus, tracheo-oesophageal fistulae and cardiac defects such as patent ductus arteriosus, ventricular septal defect, pulmonary stenosis, aortic stenosis, and coarctation[5]. Most of the clinical features matched with this patient. This 3 years old male child presented with skin pigmentation, café-au-lait spot, short stature, microcephaly, ocular abnormality, undescended testes with skeletal, cardiac and hematologic

abnormalities. Moreover, he had dental caries, gingivitis and palatal pigmentation which may have association with fanconi anemia. The main FA-associated oral manifestations reported in the literature were gingivitis, periodontitis, rotated teeth and agenesis[11]. Macrocytosis is often the first

Figure 4 & 5 : absent radius, absent thumb

detected abnormality followed by thrombocytopenia and neutropenia[5]. He had bicytopenia involving red cell and platelet series. FA is screened by the presence of increased chromosomal breakage in T lymphocyte by MMC or DEB. In the higher center, complementation group analysis and mutation analysis done to confirm the diagnosis[1,5]. The diagnosis of this patient was based on physical abnormalities and hematologic findings. Screening and confirmatory tests were not done due to lack of availability and poor financial status of patient.

The treatment of FA is still a medical challenge. Current treatments include androgen administration (Oxymetholone), blood transfusions, hematopoietic growth factors administration and hematopoietic stem cell transplantation (HSCT)[3]. 50% of patients will respond to Oxymetholone[1]. Unfortunately, it is also not available in local market. He had no ability to go to higher center. Now he is on steroid and blood component therapy on demand basis.

Conclusion

The differential diagnosis of Fanconi anemia should be kept in mind if a patient present with hyperpigmentation of skin, skeletal abnormalities along with pallor. Early diagnosis and HSCT can provide long term disease free survival. Pancytopenia, dysplastic marrow and multiple congenital anomalies may be a clue to diagnosis in a center which has no facility to do advanced tests. But good financial condition and advanced institutional support is pre requisite for standard treatment.

Disclosure

All the authors declared no competing interest.

Reference

1. Lanzkowsky P. Manual of Pediatric Hematology and Oncology. 5th edition. London: Elsevier 2011:138-147.

2. Dror Y, Freedman MH. The Inherited Pancytopenias. In. Kliegman RM, Stanton BF, Geme JW, Schor NF, Behrman RE eds. Nelson textbook of Pediatrics. 20th edition. Philadelphia: Elsevier Saunders 2016; 2362-2370.

3. Rage AMA, Mohamud AO and Kadle MAH. Fanconi's Anemia-Rare Aplastic Anemia at Ten Year-Old Boy in Mogadishu-Somalia: Case Report. Case Reports in Clinical Medicine 2015; 4: 271-275.

4. Solomon PJ, Margaret P, Rajendran R, Ramalingam R, Menezes GA, Shirley AS et al. A case report and literature review of Fanconi Anemia (FA) diagnosed by genetic testing. Italian Journal of Pediatrics 2015; 41:38.

5. Tischkowitz MD. Hodgson SV. Fanconi anaemia. J Med Genet 2003;40:1-10

6. Unal S, Ozbek N, Kara A, Alikas M, Gumruk F. Five Fanconi Anemia Patients With Unusual Organ Pathologies. American Journal of Hematology 2004;77:50-54

7. Taniguchi T, D'Andrea AD. Molecular pathogenesis of Fanconi anemia: recent progress. Blood 2006;107; 4223-4233

8. Mohanty D. Understanding complexity of Fanconi anaemia. Indian J Med Res 2016; 143: 132-133.

9. Lee HJ, Park S, Kang HJ, Jun JK, Lee JA, Lee DS et al. A Case Report of Fanconi Anemia Diagnosed by Genetic Testing Followed by Prenatal Diagnosis. Ann Lab Med 2012;32:380-384

10. Wajnrajch MP, Gertner JM, Huma Z, Popovic J, Lin K, Verlander PC et al. Evaluation of growth and hormonal status in patients referred to the International Fanconi Anemia Registry. Pediatrics 2001;107:744-54.

11. Falci SGM, Faria PC, Tataounoff J, Santos CRR, Marques LS. Fanconi's anemia in dentistry: a case report and brief literature review. Rev Odonto Cienc 2011;26(3):272-276