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Fanconi's Anemia among Sudanese Children: A Report of Forty Cases

Abstract

Background: Fancon's Anemia (FA) is a rare genetic condition characterized by various developmental defects and bone marrow failure due to specific DNA mutation. It carries an increased risk of malignancy. The gold standard test for (FA) diagnosis is chromosomal breakage hypersensitivity to alkylating agents. There are no published data about FA among Sudanese children. The aim of this study is to review the demographic features, clinical presentation, treatment given and outcome of Sudanese children with FA admitted to a major pediatric hospital from January 2010 to January 2015.

Methods: The medical records of patients with (FA) admitted and followed at a major pediatric hospital in Khartoum state was reviewed retrospectively.

Results: A total of 40 patients with confirmed diagnosis of FA were identified. The mean age of patients was 12±2.5 years. The common age at presentation was 5-10 years. The majority of cases were from Western Sudan (40%). Consanguinity was present in 72.5% of the patients. 80% of patients presented with bleeding. Common clinical signs were skin pigmentation (80%) and skeletal deformity (65%). All cases revealed pancytopenia and hypo-cellular bone marrow. 35% of patients died with no gender predilection. Most of deaths occurred in the age group of 10-15 years (58.3%). The most common causes of deaths were bleeding (57.1%) followed by leukemia 35.7% and infections 7.1%. All patients received Danazol with variable response. No patient received bone marrow transplantation.

Conclusion: FA in Sudanese children presents with skeletal deformity and pancytopenia with a high rate of consanguinity. It affects commonly males between ages 5-10 years. The most common cause of deaths was bleeding followed by malignant transformation. The problem was associated with a poor outcome.

Keywords: Fanconi's Anemia; Sudanese; Children; Hyper pigmentation; Skeletal deformities; Pancytopenia

Research Article

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Abbreviations: FA: Fanconi's Anemia; BMF: Bone Marrow Failure; AML: Acute Myelogenous Leukemia; DEB: Diepoxybutane; HSCT: Hematopoietic Stem Cell Transplant; TWBC: Total White Blood Cells; HB: Hemoglobin; BMT: Bone Marrow Transplant

Introduction

Fanconi's anemia (FA) is the most frequent inherited cause of Bone Marrow Failure (BMF) [1]. It is transmitted through both autosomal and X-linked recessive modes [2]. It affects all ethnic groups. It is characterized by congenital malformations, progressive marrow failure and predisposition to acute myelogenous leukemia (AML) and other malignancies [3]. The hypersensitivity to DNA cross-linking agents such as diepoxybutane (DEB) is used as a diagnostic test for this disease. Currently Hematopoietic Stem Cell Transplantation (HSCT) is the best treatment to cure severe aplastic anemia [4,5]. This study aimed to review the demographic and clinical features of FA and to assess their outcome.

Method

This is a descriptive, retrospective, hospital based study done at Gaffer IBN Oaf specialized pediatrics hospital, a major hospital in Khartoum state, during January 2010 to January 2015. Children of both sexes 17 years old or younger who met the following case definition of FA and had complete records were included in the study. Case definition of FA: patients who had one or more of the following clinical features: short stature, microcephaly, deep seated eyes, café au lait spot, hypo or hyper pigmentation and skeletal deformity with pancytopenia and hypo cellular bone marrow with or without chromosomal breakage or positive family history. Data was retrieved from the patients' medical records. A data collection sheet was designed to record the study variables. It contained the personal data, symptoms and signs, family history, past medical history, investigations, management and outcome. The Outcome measured was: Death, number of admissions, recovery from disease and bone marrow transplantation. The data collected was processed using statistical package for social

sciences (SPSS). Chi square test was used to assess the significance of statistical difference in categorical data. P value of less than 0.05 was considered as significant. Mean and standard deviation were presented where applicable. Results were presented as tables and figures. Ethical approval was obtained from the research committee of the hospital involved in the study.

Results

A total of 40 patients with FA were identified. Males were 25 (62.5%) with a male to female ratio of 1.7:1. The mean age of the study population was 12.0±2.5 (5.0-14.5) years with no statistical significant difference in age between males (mean age 7.6 years) and females (mean age 6.5 years) (P value=0.713). The majority of patients were from Western and Northern Sudan (Table 1). And most patients were 5-10 years old (Table 2). Family history of congenital malformation was present in 8 patients (20%), blood transfusion in 2 patients (5.0%) and cancer in another 2 patients (5.0%).Consanguinity (first cousin) was present in 72.5% of patients. The first presentation was due to mucocutaneous bleeding in (80%) of cases, pallor in 12%, leukemia in 5% of patients and 3% presented with skeletal deformity. The mean weight was 17.3±7 kg. 30 patients (75%) had weight below 3rd centile, while 25% had normal weight. The mean weight for males was significantly higher than that for females (19 kg Vs 14 kg) P value =0.049). The mean height was 111.3±16.8 cm, 32 patients (80%) had stature that fall below 3rd centile, while 20% were of normal stature. The mean height for males was significantly higher than that for females (117cm Vs 104cm). (P value =0.013). The mean head circumference was 47.5±3.3cm. 82.5% of patients had a head circumference below the 3rd centile while 17.5% had normal head circumference. The mean head circumference for males and females were comparable (48cm Vs 46 cm) (p value =0.149) (Table 3).

Table 1: Geographical distribution of patients with Fanconi's anemia (N=40).

Geographical area	Frequency	Percent
Western Sudan	16	40
Northern Sudan	11	27.5
Eastern Sudan	7	17.5
Central Sudan	6	15
Total	40	100

Table 2: Age distribution of patients with Fanconi's anemia (N=40).

Age Years	Number	Per cent
01-May	7	17.5
05-Oct	21	52.5
Oct-15	12	30

Table 3: Anthropometric measurement in patients with Fanconi anemia N=40.

Measurement	Range(Mean± SD)	< 3rd Centile	Normal
Weight	8-34 (17.3±7.0)kg	30*(75%)	10*(25%)
Height	76-149(111.3±16.8) cm	32*(80%)	8*(20%)
Head circumference	41-56(47.5±3.3) cm	33*(82.5%)	7*(17.5%)

N: Number; *: Number of patients

Skin pigmentation was seen in 32 patients (80%) and skeletal deformities in 26 patients (65%) Pallor was seen in 62.5% of patients followed by wasting of thenar and hypothenar muscles (55%), eye dysmorphism in 48%, tongue pigmentation in 30%, skin bleeding in 15%, ear deformity in 10%, spine abnormalities in 2.5% and hearing loss in 1/40 (2.5%) (Table 4). Skin pigmentation was in the form of café au lait spots in 71.9% of patients, hypo pigmentation in 21.9% and diffuse pigmentation in 6.3 %. Skeletal deformities were thumb anomaly in 17/26 (65.4%) clinodactyly in 5/26 (19.2%), pes cavus in 3/26 (11.6%) and absent radius in one case (3.8%) (Table 5)(Figure 1a, 1b, 2a and 2b) The mean Total White Blood Count (TWBC) was ranged 2.02±0.618 $\times 10^9$/L); the mean of TWBCs for males was 1.9×10^9/L and for females was 2.1×10^9/L with no statistically significant difference (P value =0.495). The mean Hemoglobin (HB) concentration was 43.0±14.9g/L. The mean HB concentration for males was and for females were comparable (45g/l Vs 42g/L, P value=0.64). The mean platelet count was $12.6\pm9.976\times10^9$/L. The mean platelet count for males and for females were comparable (12×10^9/L Vs 13×10^9/L, (P value= 0.713). Pancytopenia was present in 95% of children in the study population. Red blood cell were macrocytic in 50% of cases, normocytic in 45% of patients and microcytic in 5% of patients .The mean of MCV for males was significantly higher than that for females(93.95 fl Vs 86.34 fl) P

value =0.009. Abdominal ultrasound findings: 19/40 (45%) had different pattern of renal abnormalities with ectopic kidney being the commonest (36.8%) (Table 6). Screening for hepatitis A, B and C and HIV were negative in all cases. Bone marrow examination of all cases revealed hypo cellular bone marrow, depressed erythropoiesis and mega karyocyte and granulopoiesis and fatty replacement. 28(70%) patients were tested for chromosomal breakage; 27 (96.4%) of them showed chromosomal instability. One case with typical phenotypic picture showed negative result on single testing, further testing was not performed (Table 7).

27 (67.5%) patients received Danazol as a treatment for variable duration. Those who received treatment had significantly less hospital admissions (12 Vs 47) (p value=0.001). Death occurred in 14(35%) patients; 9 of them were males (36% of the total males in the study group) and five were females (33.3% of total females in the study group. P value > 0.05 Table 8 showed the age distribution of these children. Death was due to bleeding in 8 (57.1%) children), AML in 5 children (35.7%) and one case (7.1%) died of sepsis. The interval between the diagnosis and death was 2-5 years in 7(50%) cases, 1-2 years in 5(37.7%) cases and less than one year in 2(14.3%) children. No patient received bone marrow transplant.

Table 4: Clinical signs in children with FA (N=40).

Clinical sign	Number(Percent)
Skin pigmentation	32(80%)
Skeletal deformity	26(65%)
Pallor	25(62.5%)
Wasted thenar and hypothenar muscles	22(55%)
Eye dysmorphism	19(47.5%)
Tongue pigmentation	12(30%)
Skin pigmentation	6(15%)
Ear abnormality	4(10&)
Spine deformity	1(2.5%)
Hearing loss	1(2.5%)

N: number; FA:Fancon's Anemia

Table 5: Pattern of skeletal deformity seen in patients with Fanconi's anemia (N=26).

Type	Frequency	Percent %
Thumb anomaly	17	65.4
Absent	10	
Bifid	4	
Dangling	2	
Triphalangeal	1	
Clinodactly	5	19.2
Pescavus	3	11.6
Radial anomaly(absent)	1	3.8
Total	26	100

Table 6: Types of renal anomalies seen in 19/40 children with Fancon's anemia.

Type	Number
Pelvic kidney	7(36.8%)
Duplex kidney	5(26.3%)
Horse shoe kidney	4(21.1%)
Small kidney	2(10.5%)
Absent Kidney	1(5.3%)
Total	19

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Table 7: Complete blood pictures in children with (FA) (N =40).

Parameter	Range(mean)	Males(mean)	Females(mean)	P value
TWBC 109	0.5-3.1(2.02±0.62	1.9	2.1	0.495
Hemoglobin g/l	21-73(43±14.9)	45	42	0.69
Platelets 109	1-40(12.6±9.98)	12	13	0.713
MCV fl	65-104(98±13.55)	93.95	86.34	0.009

N: Number

Table 8: Age distribution of children who died with fanconi's anemia.

Age	Death		Total
	Death	No death	
1-5 years	1 (14.3%)	6 (85.7%)	7 (17.5%)
5-10 years	6 (28.6%)	15(71.4%)	21(52.5%)
10-15 years	7(58.3%)	5(41.7%)	12 (30%)
>15 years	0	0	0
Total	14 (35%)	26(65%)	40 (100%)

P value = 0.102

Figure 1a: Absent right thumb.

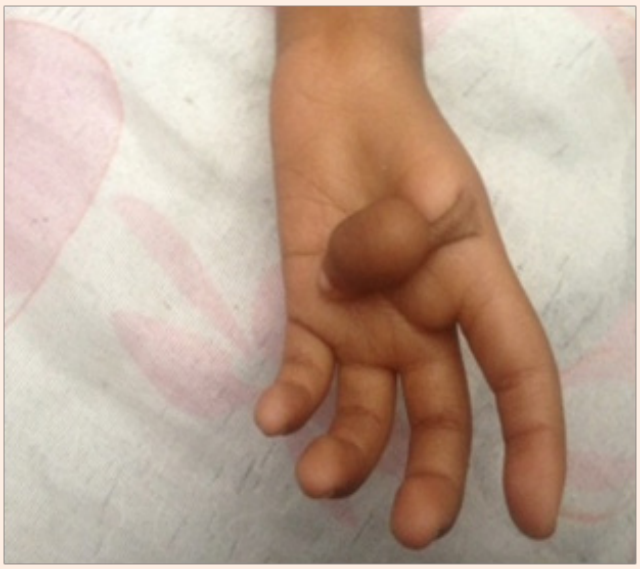

Figure 1b: Dangling thumb of the left hand (same patient in Figure 1a).

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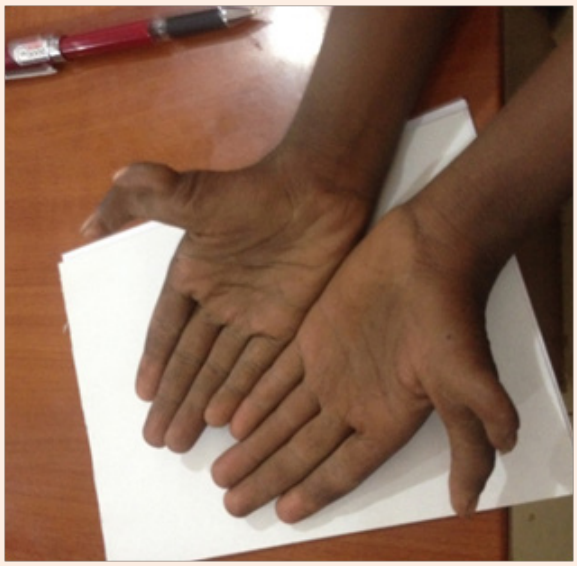

Figure 2a

Figure 2b

Figure 2a: Bilateral digitalized bifid thumbs, hyper pigmentation of the palm, wasted thenar and hypothenar muscles.

Figure 2b: Hyper pigmentation (same patient in figure 2a).

Discussion

This is the first report on Fanconi's anemia in Sudanese children .The study had shown that most of the patients belonged to tribes from Western Sudan. Many tribes from the West moved to Khartoum state during the wave of drought that stroke that area; this might explain partly their predominance in this study. First cousin marriage rates in Sudan are amongst the highest worldwide reaching 40-45% of all marriages [6-8]. First cousin marriage was present in 72.5% of cases (much higher than the above mentioned national rate). This is double the rate reported from India [9] but comparable to the rate reported from Turkey [10]. Family history of similar disease and/or blood transfusion was present in one third of the studied population, a rate far higher than that reported from Korea [11]. This in addition to the high rate of consanguinity supported the genetic nature of the disease. The mode of inheritance of FA in this study is probably an autosomal recessive which is the commonest pattern of inheritance in this disease [1].

Male gender predominated in this study, which was similar to what was reported by Shimamura A, et al. [1]. Equal sex affection was reported from Italy [12] and female predominance was reported from Tunisia [13] and South Africa [14]. The mean age of children when FA was diagnosed was similar to that reported from Tunisia [13].The majority of children in this study were in the age group between 5-10 years reflecting the age at which BMF occurs. Skeletal deformities (Thumb deformity, radial ray and vertebral scoliosis) were present in the majority of patients. The rate reported in this study was comparable to that reported by Dokal I [15] and Shimamura A, et al. [1]. Despite this high rate of abnormalities they were rarely the initial presenting symptoms. This could be due to the fact that these anomalies were not considered by parents as major defects that warrant consultation.

Skin pigmentation was the most common clinical sign (80%). This was low compared to the rate reported from Korea [11] but higher than the rate reported by Shimamura A, et al. [1] and Dokal I [15]. Skin pigmentation included cafe au lait spots, hyper pigmentation and hypo pigmentation. The dark skin of Sudanese children might have affected the rate of detection of these changes. Short stature was present in 80% of patient with girls being more affected than males. This rate was higher than that reported by Dokal I [15]. The weight was similarly affected. Poor nutrition could be another factor that affected the growth of these patients as most of them belonged to poor families. Small head was present in the majority with males and females being equally affected. This rate was higher than that reported in the Literature [1]. It is important to note that endocrinolgical work up was not carried in this study to see its contribution to growth failure.

Renal abnormalities were detected in almost half of the patients which was high compared to what was reported in the literature [1,16,17] .The high incidence of renal anomalies in this study emphasized the need for a renal ultra sonographic evaluation in all Sudanese patients diagnosed with FA or aplastic anemia. Furthermore apparently normal children who were found to have renal anomalies should have a detailed history and careful clinical examination to rule in or out FA. Eye dysmorphism was present in half of the patients, a rate higher than that reported by Dokal I [15] and Shimamura A, et al. [1] as well as that reported from Korea [11].

The rate of hearing loss reported in this study was low compared to that reported by Dokal I [15] and Shimamura A, et al. [1]. Routine screening was not carried for financial reasons. Mucosal bleeding was the first and most common presentation in Sudanese children with FA; this is not different from what was reported in the English literature [18,14]. The rate of pallor reported in this study is lower than that reported from Tunisia [13]. Pancytopenia was present in 95% of cases of FA among the study populations as initial hematological findings. Pancytopenia, as an initial hematological finding, was found in 53 % of patients in the International Fanconi Anemia Registry Study [19]. This high rate is not surprising since most of our patients presented late when bone marrow failure was well established.

The frequency of leukemia in this study was 12.5 %. This is comparable to that reported from Korea [11] but half the rate reported from India [9]. Leukemia as an initial presentation was present in 5% of the study population. This is double the rate reported in the International Fanconi Anemia Registry Study [19]. Acute myeloid leukemia was the commonest type. Bone marrow examination of all cases revealed hypo cellular bone marrow, depressed erythropoiesis and mega karyocyte and granulopoiesis at the time of diagnosis; this is similar to several reports in the literature [1,11,13]. Two cases showed evidence of acute myeloid leukemia on top of hypocellularity. Cytogenetic studies were not carried on bone marrow samples due to lack of this facility. Two third of the patients were tested for chromosomal breakage to confirm the clinical diagnosis of FA. All were positive for chromosomal instability except one patient who tested negative despite he had phenotypic features of the disease (skeletal abnormalities and hyper pigmentation). In a Korean study one patient carrying the FA mutation gene tested negative for chromosomal breakage [20].

Two third of the cases had received Danazole as a treatment. Patients who received treatment had statistically significant reduced frequency of hospital admissions. A study from South Africa showed that an adequate trial of androgen therapy led, in 48% of cases, to an increase in their initial HB concentration by more than 2g/dl or return to normal, most of patients subsequently required intermittent course of androgens and 12% were able to stop androgen and maintain normal HB concentration [14]. None of our patients received Bone Marrow Transplant (BMT). In the report from Tunisia [13] also no patient received BMT. In Korea 81% of patients underwent transplantation [11] while in Italy 57% received BMT [12]. In this Italian study it was observed that the survival of the transplanted and non-transplanted were not different [12]. BMT is a very expensive mode of therapy and thus not available in countries with limited resources like Sudan. One third of patients died in this study. Death was more common among the age group of 10-15 years. The majority of cases died 2-5 years from diagnosis. The common causes of death were bleeding followed by leukemia; sepsis was the least cause of death. This is different from the outcome reported from South Africa where malignancy was the leading cause of death followed by sepsis [14].

Conclusion

FA is not uncommon in Sudan. It was associated with high degree of first cousin marriage. Skeletal anomalies, skin pigmentation and renal anomalies were common features. Patients presented when bone marrow failure was well established. Bleeding was the commonest cause of death. Further studies are required to determine the mutated genes in this population.

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