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Fanconi anaemia;The Libyan Experience.

Hala Elbishti[1], Amna Rayani[2], FathiaAl Rayani[3], Fathia Elmurabt[4], Elmukhtar Habas[5].
Correspondent author: AmnaRayani, E mail: amnnarayani@yahoo.com
1- Consultant Paediatrician, Zawyia Hospital,ZawyiaUniversity
2- Consultant Paediatric Haematology, Tripoli Children Hospital,Tripoli University, Medical faculty.
3- ConsultantpaediatricHaematology, Tripoli Medical Centre, Tripoli University, Medical faculty.
4- Consultant Neonatology,Zawyia Hospital. Zawyia University
5- Consultant physician, nephrology, Tripoli Central Hospital, Tripoli University, Medical faculty.

Abstract:

Background:
Fanconi anemia (FA) is one of inherited anemias, leading to progressive bone marrow failure (BMF). It manifests usuallyduring early childhood and adolescent. It is one of congenital diseases affects most of body organs and predispose to malignancy.

Objective:
To study the prevalence of FA and its clinical course in Libyan patients.

Methods:
A retrospective study of Fanconi anemia,diagnosed patients who were followed up at hematology department during twenty- one years, were reviewed.

Results:
Seventy five children were diagnosed as Fanconi anemia patientsin Tripoli Medical center hematology department. Forty seven patients (63%) of them were diagnosed at median age of7years and 6 months (5-10 years) and the other 37% median age wasolder than 7 years.Forty two patients were male and 33 patients were female with male: female ratio of 1.27:1. History of consanguine marriage was reported in 46% of patients. Other family member with same disease reported in 64% of patients. Fifteen patients (20%) were asymptomatic at presentation, bone marrow failure symptoms reported in 60 patients (80%). Sixty- three patients (84%) had somatic abnormalities. Fifty per cent of patients responded to treatment in the 1st year, and eventually become refractory to treatment by 3-5 years. Forty five patients (60%) had complications related to treatment, 5 patients died because of malignancy, and one patient diedby end stage renal disease.Five patients were transplanted with HLA compatible donor. Prognosis in the transplanted patients was variable with a median survival age was 15 years.

Conclusion
FA appears common in Libyan population. Family counselling, early diagnosis and treatment are crucial to prevent Fanconi anemia and its complications.

Key words:*Fanconi Anaemia,consanguinity,malignancies, Libyans.*

Introduction

BMF syndromeis a group of acquired and/or inherited diseases. FA is one of reported diseases that lead to BMF. FA is an autosomal recessive inherited disorderfirstly described in 1927. It is characterized by a reduction ofall the three blood cell lines in the body. [1-3] FA patients are usually smaller and shorter than average. FA, dyskeratosiscongenita, Shwachman-Diamond syndrome, Diamond-Blackfan anemia, amegakaryocytic thrombocytopenia are inherited diseases.[2-3]FA is the most frequently reported inherited BMF syndromes.FAassociates with congenital anomalies, skin discoloration, thumb deformities, microcephaly, cardiac and renal congenital defects, and it increases risk of malignancies. [4,5,6,7,8] FA is considered as chromosome breakage disease that means individuals affected with this disease have an increased rate of breakage and rearrangements along their chromosomes. FA incidence was approximately 3 case/ million, and the heterozygote frequency was estimated in the USA and Europa at 1 in 300. FA was reported in many ethnic groups, and special different mutations reported in Ashkenazi Jews with a carrier frequency of about 1 in 89, and Afrikaners carrier frequency was estimated as 1 in 83.[9,10,11,12] FA frequency is higher in malethan infemale (1.2:1), although equal ratio is expected in autosomal recessive disease. FA has autosomal recessive mode of inheritance, and has higher carrier frequencies in Ashkenazi and Afrikaner than other races.[7] FA patients have high risk to develop BMF, aplastic anemia, myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and epithelial malignancies and renal failure. [12]Renal failure is less frequent with anestimated occurrence rate of 25 - 30% especially in FA patients who diagnosed late. [14]

FA is a heterogeneous condition presents with a different congenital defects that invariably results in defective hemopoiesiswhich is the major cause of morbidity and mortality. Treatment of hematologicalcomplications of FAby stem cell transplants is a new advance inFA treatment. Solid tumor asesophageal, vulval, and oropharyngealtumours are common in survivorsof the hematological complications in FA patients. Up to our knowledge, there werenot any published data or study about FA in Libya therefore; we studied the available filesof patients who diagnosed as FA patients in main referral hospital at Tripoli - Libya.

Method

Medical records of all outpatients and inpatients who were diagnosed hadFAover period of 21 years were reviewed regarding socio-demographic feature,clinical presentation, hematological abnormalities,characteristic somatic features and complications detected at presentation or occurred during follow up. Diagnostic measures include CBC, reticulocytes count, bloodfilm,bone marrow aspiration and biopsy, hemoglobin (Hb) electrophoresis(Hb F level),liver function test,renal function test. U/S abdomen, echocardiography,and chromosomal breakage test (last 2 years). Treatment applied, complications, and outcome were analyzed. All patients received steroids and oxymethalone.All investigations were done at hematologydepartment at Tripoli MedicalCenterand Bioscentia-Germanylaboratories.

Results:

Seventy five children whoreferred from different cities of Libya were diagnosed havingFAat Tripoli Medical Center at Tripoli –Libya.Analysis of demographic data demonstrated; 42 patients were male (56%), and 33 patients female (44%) with a ratio of 1.27:1.Patients' age at presentation showed different pattern; 9.3% of patients diagnosed before 5 years of age, 47 patients (62.7%) diagnosed while they were aged between 5 – 10 years, and the rest (21 patients 28%) were aged more than 10 years. All of the patients were Libyan (98.7%) except one patient was Palestinian (table 1).

Clinical parameter		No of patients	%
Sex	Male	42	56
	Female	33	44
Age	<five years	7	9.3
	>five to ten years	47	62.7
	More than ten years	21	28
Nationality	Libyan	74	98.7
	Palestinian	1	1.3

Table 1. Distribution of the patients according to their age, sex and nationality

Consanguine marriage history reported in 46%. Another family member had FA reported in 64% of patients. At presentation, 60 patients (80%) had symptoms related to BMF such as dyspnea, fatigability, generalized tiredness etc. fifteen 15 patients (20%) were asymptomatic.

Sixty three patients (84%) had somatic and internal organs abnormalities. Short stature reported in 61%, failure to thrive in 28 patients (37%), skeletal abnormalities such as - Hypo plastic thumb, super numeral thumb, club foot, absent thumb, congenital heart disease (CHD)in 28 patients (37%). Hyper and hypo-pigmented skin lesion reported in 23 patients (31%). Congenital eye lesions as; small eye, squint, ptosis, hypertelorism,and blue sclera in 12 patients (16%). Kidney congenital abnormality as ectopic kidney, horse shoe kidney, hypoplastic kidney, both kidneys located at one sideand undescended testis in 12 patients (16%). Other congenital abnormalities in heart, endocrine, ear and face were reported (table 2).

Congenital anomalies		**NO:**	**%**
Short stature		46	61
Failure to thrive		28	37
Skin abnormalities	Hyper pigmentation (Café au lait spots)	23	31
Skeletal abnormalities	Hypo plastic thumb, super numeral thumb , club foot, absent thumb, CHD,poly dactyls, increase curvature of little finger	28	37
Ophthalmological abnormalities	Micro ophtalamia, squint, ptosis, hypertolarism, blue sclera	12	16
Renal abnormalities	Ectopic kidney , horse shoe kidney, hypoplastic kidney, both kidneys in one sides, undescended tests	20	27
Cardiac abnormalities	VSD, MR, Epstein anomalies	8	11
Endocrinal abnormalities	Growth hormone deficiency	3	4
Microcephaly		18	24
Deafness		3	4
Dysmorphic feature (triangular face, fine face feature, micrognathia)		22	29
Mental retardation		5	7
Gastrointestinal abnormalities		2	3

Table 2. Congenital anomalies associated Fanconi anaemia patients.

CBC of patients showed pancytopenia in 55 patients (73%), low platelets in 16 patients (21%), macrocytosis in 67 patients (89%), and low reticulocyte count in 28 patients (37%). Bone marrow aspiration was reported hypocellular in 70 patients (93%) and hypoplastic bone biopsy reported in 7 patients (9%) table 3.

Parameter		**No of pts**	
C.B.C	Pancytopenia	55	73
	Isolated leucopoenia	1	1
	Thrombocytopenia	16	21
	Normal C.B.C	3	4
M.C.V	Macrocytosis	67	89
	Normal M.C.V	8	11
Reticulocyte count	Low	28	37
	Normal	8	11
	No data	29	39
Bone marrow aspiration	Hypocellular	70	93
	Reactive bone marrow	2	3
	Abnormal cells in bone marrow	0	0
	No data	3	4
Bone marrow biopsy	Hypo plastic bone marrow	7	9
	No data	68	91
HB-electrophoresis	High HF level	39	52
	Normal HF level	3	4
	No data	33	44

Table 3. Haematological abnormalities detected at presentation

Out of 75 patients only 26 patients had chromosomal study found in their files. Out of the 26 patients 24 patients had positive chromosomal breakage test and 2 had negative chromosomal breakage (figure 1).

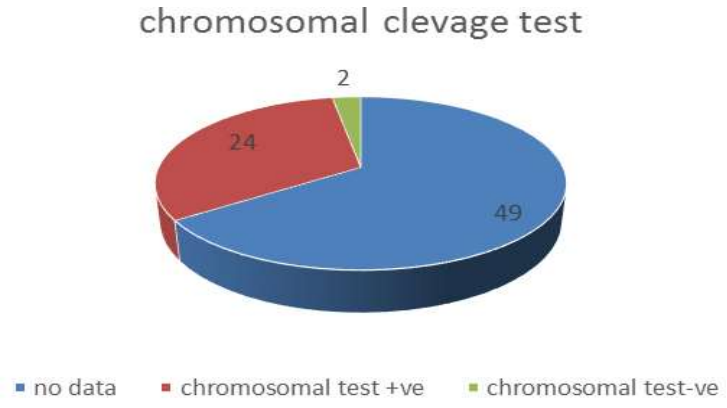

Figure1. Chromosomal breakagetest chart.

Patients presented with bleeding diathesis and needed admission were 65 patients (87%).Forty five patients (60%) had complications related to treatment as Cushnoid feature in 11 patients (15%) andhirsutism. Increased blood pressure and blood sugar reported in 8% and 4% of patients during treatment period respectively. Recurrent infection reported in 4%, and hepatitis B virus (HBV) infection in 8% of patients. Chronic renal failure (CRF) with renal osteodystrophy and bone fracture reported in one patient (table 4).

Complications	Number of patients	%
Bleeding diathesis	65	87
Cushnoid face	11	15
Hirsutism.	11	15
High blood pressure	6	8
High blood sugar	3	4
Recurrent infection	9	12
Hoarseness of voice	3	4
Irregular menses	7	9
A septic necrosis of femoral head	1	1
GVHD(graft versus host disease)	1	1
Chronic renal failure(renal osteodystrophy, multiple fracture)	1	1
High ferritin level	2	3
HBV infection	6	8

Table4. List of complications of FA treatment

Half of the patients respond to treatment during the 1st year, and eventually become refractory to treatment after 3-5 years. Five patients were died by malignancy, one patient died due to chronic renal failure. The prognosis was variable from patient to patient and the median survival age was 15 years. Five patients were transplanted with HLA compatible donors and still alive.

Discussion

FA is the most frequent reported rare inherited BMF syndromes, with approximately 2000 cases world-wide reported in the medical literature upto Feb 2016. In our study, 75 patients were followed in the major referral center in Libya. Libyan population was around 6 million, and about 2/3 of the Libyan population leaving in Tripoli and cities around it. This means that about one

case per 100.000 of our population has FA, and about 3.7% of the reported cases world-wide present in Libya. This predominance of FA in Libya mostly due to abundance of first and second degree marriage between families. FA accounts for approximately 25% of aplastic anemia cases that characterized by macrocytic anemia, leukopenia and thrombocytopenia. In our series, 73% of the patients had pancytopenia and macrocytic anemia in 89% of patients and low reticulocyte count in 37% of patients, 21% of patients had thrombocytopenia and 93% of patients had hypocellular bone marrow. However, the percentage of aplastic anemia appears more reported in this study, but itis not significantly different from worldwide reported data. These differences may be due to late presentation of our patients. About 75% of FA patients have a minimum of one physical anomaly, approximately 25% ofFA patients havemultiple congenital abnormalities. Short stature is the most frequent reported abnormality in this study (61%) -height below 10th percentile - and other skeletal abnormalities than that reported in previous studies. [15,16] . Shortstature and failure of growth might be due low response to growth hormone,hypothyroidism and impaired glucose tolerance.[17] Minor bleeding, severe hemorrhages, infections, leukemia, myelodysplastic syndrome, liver tumors, and other cancers are a known complications in FA patients. [18]In our study, bleeding was the commonest complication (87%). Bacterial infection and viral infection such as HBV infection had been reported in this study either at presentation or at treatment period. Acute renal failure occurred in one patients in this study. The renal failure in our patient might due to septicemia or mostly due to treatment side effect as dehydration due to chemotherapy. It was reported that about 9% of FA patients developed leukemia, and most of them develop acute myeloid leukemia[19]. Myelodysplastic syndrome was reported in 7% of patients. In this series leukemia was reported in about 6% of patients.

Conclusions

It seems that FA is a prevalent in Libya. This increase of FA might be due to high incidence of marriage between related families' members. Hence, carrier screening and genetic counseling to those families at riskare needed to prevent FA further occurrence and it complications.

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