Fanconi and Non-Fanconi anemia: A Single Center Experience of A Large Egyptian Cohort

Original Article

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ABSTRACT

Background: Bone marrow failure syndromes are a group of diseases that could be inherited as congenital or acquired aplastic anemia. Fanconi anemia (FA) is the commonest cause of congenital aplastic anemia.

Aim: This study reports patients with congenital aplastic anemia aiming to reveal the clinical and cytogenetic differences between the two groups, (non-Fanconi and Fanconi anemia) also to compare between patients included in this study with those from different ethnic populations.

Patients and Methods: 204 patients with aplastic anemia were included (101 non-Fanconi and 103 Fanconi). Induction of chromosomal breakage by DEB was done to all patients to confirm the diagnosis of FA and to determine the degree of chromosomal breakage.

Results: Mean age of non-FA and FA patients was 10 ± 4.24 and 9 ± 4.61 years respectively with high consanguinity rate (65% 79% respectively). 24.7% of non-FA patients exhibited very severe aplastic anemia, while the majority (72.2%) exhibited severe aplastic anemia. Few patients (1.9%) had non-severe form. While, in FA patients, very severe aplastic anemia was present in 10.6%; 84.4% had severe form and 4.8 % had non-severe form. These results were significant between the two groups (*p=0.02*). 12.6% of FA patients showed mosaic DEB results. Comparing FA cases with one cell line and those with two cell lines regarding patients' percentiles, hematological abnormalities and degree of severity revealed no significant difference.

Conclusion: This study reports a large number of Egyptian patients diagnosed as congenital aplastic anemia with relatively high number of FA patients due to higher rate of consanguinity in Egypt. FA accounts for a significant percentage of congenital aplastic anemia and should be ruled out stressing on congenital anomalies and hematologic findings. Further evaluation of patients who share similar phenotypes and genetic studies are highly recommended to identify the dominant FA types in Egypt.

Key Words: Aplastic anemia, Egyptian, Fanconi anemia.

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INTRODUCTION

Bone marrow failure syndromes (BMFs) are a broad group of inherited or acquired diseases defined by decreased production of one or more of the major hematopoietic lineages. Inherited BMFS are caused by mutations which may be passed down from parents or arising de novo and they form 10 - 15% of all BMFS and 30% of pediatric BMFS, with an average of 65 cases per million live births each year. The etiology of nearly 75% of these children is not yet identifiable. The most common inherited BMFS include; Fanconi anemia, congenital amegakaryocytic thrombocytopenia, Shwachman-Diamond syndrome, and reticular dysgenesis (inherited in an autosomal recessive pattern), dyskeratosis congenital (inherited in an X-linked recessive pattern), Blackfan-Diamond anemia and reticular dysgenesis (inherited in an autosomal dominant pattern) (**Elmahdi and Kojima, 2017; Moore and Krishnan, 2021**).

Fanconi anemia (FA) is considered to be the most common inherited BMFS, which is characterized by pancytopenia and it may affect all the body organs. It is inherited as autosomal recessive; however in 2% of cases the inheritance is X-linked recessive (in homozygous or heterozygous patterns). It has an incidence of 1 – 5 cases per million and the frequency of carrier is 1 in 200-300 (**Moore and Krishnan, 2021**).

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Fanconi anemia patients may suffer from breath shortness, chest pain, fatigability, and dizziness in addition to epistaxis, petechiae and prolonged wound bleeding as a result of thrombocytopenia, and recurrent infections are usually present with severe leukopenia. Average of 75% of FA is associated with birth defects. On physical examination; short stature, café-au-lait patches and structural abnormalities of extremities are commonly present. Other findings include microcephaly, frontal bossing, micrognathia, low hairline, webbing and shortening of the neck, in addition to hydrocephalus, scoliosis, spina bifida, ribs abnormalities and extra vertebrae (**Bhandari *et al*., 2021**).

Patients with Fanconi anemia have a higher chance to develop lymphomas, head and neck squamous cell carcinoma, GIT and brain tumors), in addition to hematological malignancies like acute myeloid leukemia (**Jacquemont and Taniguchi, 2007**).

More than 23 FA complementation genes have been described to date all of which have a role in the repair pathway of DNA. The majority is inherited as autosomal recessive except FANCB (X-linked) and FANCR (RAD51) (autosomal dominant) (**Bhandari *et al*., 2021**). Disruption to the FA pathway has been found to impair DNA repair mechanism resulting in the characteristic cellular FA features of increased induced chromosome breakage and hypersensitivity to inter-strand cross-linking agents (**Feben *et al*., 2017**).

Diagnosis could be delayed till the development of bone marrow failure. The average age of presentation is seven years. Yet, with the increased awareness and enhancement of prenatal screening; earlier diagnosis has been reported (**Bhandari *et al*., 2021**).

The most adopted diagnostic test for FA is the chromosomal breakage test using diepoxybutane (DEB) (1,3-butadiene diepoxide), as it has the highest specificity and sensitivity. Molecular work-up should follow to identify the patient complementation group and to detect the pathogenic variant (**Auerbach, 2015**).

We present here the first report of Egyptian aplastic anemia and Fanconi anemia registry during the period from 2015 to 2020 (5 years), aiming to reveal the clinical and cytogenetic differences between the two groups, also to compare between the patients included in this study with those from different ethnic populations.

PATIENTS AND METHODS:

The study was approved by the Ethical Research Committee of National Research Centre (NRC), and was conducted in accordance with NRC by laws for human research. It conforms to the provisions of the Declaration of Helsinki in 2000 and its updated version in 2013. Parents or caregivers gave written informed consent to the study.

a- Patients

This study was conducted in the period from 2015 to 2020 (5 years) and included 204 patients recruited from the clinical genetics department and referred to the Human cytogenetics department of the National Research Centre (NRC). All patients were subjected to detailed history (including demographic data, age at the onset, detailed pedigree construction and analysis with special emphasis on parental consanguinity and similar disease in the family). The clinical records of the patients were reviewed to obtain the following data: Complete blood count (CBC), bone marrow biopsy, frequency of blood transfusion, radiological studies and Electroencephalogram (EEG). The inclusion criteria for the study included a) patients' selection depending on the clinical criteria of FA like: short stature, café-au-lait patches, microcephaly, frontal bossing, micrognathia, low hairline and webbing and shortening of the neck. b) Absence of any combined congenital disorders observed clinically. c) Absence of active infections. d) Laboratory investigations consistent with aplastic anemia. e) Cytogenetic confirmation of FA. While the exclusion criteria were a) Presence of associated congenital anomalies. b) Presence of active infections.

b- Methods

Induction of Breakage by 1,3-Butadiene diepoxide (DEB) was done to confirm the diagnosis of FA and to determine the degree of the chromosomal breakage. DEB was added to the culture 24 hours after its initial, in final concentration of 0.1 µg/ml culture media. The concentration found to be specific for the induction of breakages in normal and instability syndromes. Giemsa stain only non-banded technique was used. For each case, at least 50 metaphases were scored. The slides were scored for breakage and presence of isochromatid exchange which were considered as the hallmark for the diagnosis. (**Auerbach, 2003**)

According to the result of the DEB test, patients were divided into two groups: non-FA (with negative DEB test, Group 1) and FA (with positive DEB test, Group 2).

c- Statistical analysis

Analysis of data was performed using IBM® SPSS® (Statistical Package for Scientific Studies) version 23 for Windows, copyright of Eco soft Inc. V.S (1989–2007). Description of the quantitative variables was presented in the form of means, and standard deviations (SD). Description of qualitative variables was in the form of numbers (No.) and percentages (%). Comparing means of the quantitative variables between the two groups were

carried out after data were explored for normality using Shapiro-Wilk tests of normality. Whenever the results of the test indicated that the data were normally distributed, the independent Student's t-test (parametric tests) was used to carry out the comparisons, otherwise when the data were not normally distributed comparisons were carried out using Mann Whitney test (non-parametric tests). Chi-Square test (χ^2) was used to detect the independence between groups and the qualitative variables. Fisher's Exact Test was used instead of Chi-square test when one expected cell or more were ≤ 5. Results were expressed in the form of *p-values*, and the level of significance was set at $p \leq 0.05$.

RESULTS:

This study included 204 patients diagnosed as aplastic anemia with an average annual incidence of 40 cases /year. Patients were then classified by DEB test into two groups; 101 non-Fanconi patients (DEB –ve) and 103 Fanconi patients (DEB +ve). The mean age at the onset was 6.44 ± 1.6 for the non-Fanconi group and 6.106 ± 1.606 for the Fanconi group, while the mean age at diagnosis was 10 years ± 4.24 SD for the non-Fanconi group and 9 years ± 4.61 SD for the Fanconi group. Regarding consanguinity, there were 56 non- consanguineous parents and 148 consanguineous parents among both patients groups, 55.4% of the consanguineous parents showed positive DEB test results which had a high statistical significance (*p-value = 0.028*). Gender was almost equally distributed between the two groups which was confirmed by the insignificant result (*p-value = 0.394*). Positive family history was found in 70.7% of the FA group with a high statistically significant *p-value = 0.005* (Table 1).

Clinical examination

The clinical features of both non-Fanconi anemia patients (group 1) and Fanconi anemia patients (group 2) were listed in table 2. Fanconi anemia patients (group 1) showed more significant affection of weight, height and head circumference (*p=0.002, 0.004* and < *0.0001* respectively).

All abnormalities including ophthalmological, nose, ear, upper limb, lower limb, skin, renal, cardiac, gastrointestinal, genital abnormalities were recorded in a significant higher percentage among group 2 patients (FA group) in comparison to group 1 patients (non-FA group) (Table 2).

Hematological parameters

Abnormalities in the hematological findings including hemoglobin levels and platelets counts were more significant in non-Fanconi anemia patients (group 2) (Table 3). Comparing the degree of severity, FA group revealed a significant difference (*p=0.02*) but there was no significant difference in the frequency of blood transfusion between the two groups (Table 4).

Cytogenetic examination

In our cohort of Fanconi anemia patients 13 out of 103 cases (12.6%) showed mosaic (two cell lines) DEB results. We compared both FA cases with one cell line and those with two cell line regarding patients' percentiles and hematological abnormalities and found no significant difference between the two groups (Table 5). Also, the frequency of blood transfusion showed no significant difference in the two groups (*p=0.1* 0.058 respectively) (Table 6).

Table 1: Comparing consanguinity, gender and other affected family members in Non-FA and FA groups

		Non-FA group (n=101) No. (% within variable)	FA group (n=103) No. (%within variable)	*P-value*
Consanguinity	Negative	35 (62.5)	21 (37.5)	0.028*
	Positive	66 (44.6)	82 (55.4)	
Gender	Male	64 (52)	59 (48)	0.394
	Female	37 (45.7)	44 (54.3)	
Other family member affected	Negative	87 (54)	74 (46)	0.005*
	Positive	12 (29.3)	29 (70.7)	

FA: Fanconi anemia, n: sample size, *statistically significant *p-value ≤ 0.05*

Table 2: Comparing the clinical findings in Non-FA and FA groups

		Non-FA group No. (% within group)	FA group No. (% within group)
Growth retardation		30 (29.7)	54 (52.4)
microcephaly		28 (27.7)	55 (53.3)
Short stature		22 (21.7)	38 (36.8)
Mongoloid facies		1 (1)	24 (23.3)
Ophthalmological abnormalities	Blepharophimosis	0 (0)	2 (1.9)
	Deeply seated eye	0 (0)	3 (2.9)
	Epicanthaic fold	5 (5)	5 (4.9)
	Hypertelorism	3 (3)	8 (7.8)
	Hypertrichosis	2 (2)	6 (5.8)
	Microphthalmia	0 (0)	7 (6.8)
	Retinal hemorrhage	1 (1)	0 (0)
	Squint	0 (0)	4 (3.9)
	Synophrous	4 (4)	10 (9.7)
Nose abnormalities	depressed nasal bridge	3 (3)	7 (7.2)
	thin long, deviated septum	0 (0)	1 (1)
Ear abnormalities	large cupped ears	3 (3)	8 (7.7)
	low set ears	4 (4)	7 (6.9)
	microtia	0 (0)	2 (2)
	SNHL	1 (1)	1 (1)
Upper limb findings	Arachnodactyly	3 (3)	1 (1)
	bilateral absent radius	0 (0)	2 (1.9)
	bilateral absent thumb	0 (0)	1 (1)
	bilateral bifid thumb	0 (0)	1 (1)
	bilateral hypoplastic thumb	0 (0)	7 (6.8)
	Brachdactyly	0 (0)	3 (2.9)
	broad thumb	0 (0)	1 (1)
	Clinodactyly	1 (1)	9 (8.7)
	digitalized thumb	0 (0)	1 (1)
	double thumb	1 (1)	2 (1.9)
	hypoplastic nails	0 (0)	2 (1.9)
	low inserted flappy thumb	2 (2)	7 (6.8)
	preaxial polydactyly	0 (0)	4 (3.9)
	simian crease	3 (3)	5 (4.9)
	soft tissue syndactyly	0 (0)	1 (1)
	unilateral absent proximal metacarpal bone	0(0)	2 (1.9)
	unilateral absent radius	0 (0)	1 (1)
	unilateral absent thumb	0 (0)	2 (1.9)
	unilateral hypoplastic first metacarpal bone and marked atrophy of proximal and distal phalanx of Thumb	0 (0)	1 (1)
	unilateral hypoplastic thumb	0 (0)	4 (3.9)
	unilateral thumb deformity	0 (0)	2 (1.9)

Lower Limb findings	arachnodactyly	1 (1)	0 (0)
	broad big toe	1 (1)	0 (0)
	clinodactyly	0 (0)	1 (1)
	hypoplastic nails	0 (0)	1 (1)
	soft tissue syndactyly	0 (0)	4 (3.9)
Skin pigmentation	Café au lait patchs	2(2)	24 (23.3)
	Hypo and hyperpigmented areas	0 (0)	4 (3.9)
	Petechia	1 (1)	11 (10.7)
	Skin hypopigmentation	0 (0)	5 (4.9)
Renal abnormalities	Bilat. Parynchymal disease with elevated kidney function	1 (1)	0 (0)
	Bilateral minimal dilated kidneys, unilateral prominent papilae with minimal change echogenicity	0 (0)	1 (1)
	Bilateral pelvic horse shoe kidneys	0 (0)	1 (1)
	Unilateral pelvic horse shoe kidney	0 (0)	1 (1)
	Unilateral pelvic kidney	1 (1)	7 (6.8)
	Unilateral renal hypoplasia	0 (0)	1 (1)
	Hematuria	1 (1)	0 (0)
	Renal calculi	0 (0)	1 (1)
	Solitary kidney	0 (0)	5 (4.9)
	Unilateral hypoplastic kidney with multiple cysts	0 (0)	1 (1)
Cardiac abnormalities	irregular beats	0 (0)	1 (1)
	mild TR, trivial mitral insufficiency	0 (0)	1 (1)
	tachycardia	0 (0)	2 (1.9)
	VSD, ASD, PDA	0 (0)	1 (1)
GIT abnormalities	elevated liver enzymes	0 (0)	2 (1.9)
	hepatitis	1 (1)	0 (0)
	hepatomegaly	2 (2)	4 (3.9)
	hepatosplenomegaly	3 (3)	0 (0)
	splenomegaly	1 (1)	5 (4.9)
Genital abnormalities	bilateral undescended testes	1 (1)	3 (2.9)
	hypospadius	0 (0)	1 (1)
	unilateral absent testis	1 (1)	0 (0)
Bleeding tendency	Bleeding gums	6 (5.9)	1 (1)
	Epistaxix	12 (11.9)	1 (1)
Other findings	EEG	1 (1)	1 (1)

Table 3: Comparing age, percentiles and hematological parameters in Non-FA and FA groups

	Non-FA group (n=101) Mean ± SD	FA group (n=103) Mean ± SD	*P-value*
Age in years	10 ± 4.24	9 ± 4.61	0.102[a]
Age at the onset	6.44 ± 1.6	6.106 ± 1.606	0.143
Weight	29.98 ± 13.74	24.34 ± 11.37	0.002*[b]
Height	127.38 ± 22.94	118.41 ± 21.02	0.004*[a]
HC	50.64 ± 3.23	48.80 ± 2.99	< 0.0001*[b]
RBCs x 1000000	2.81 ± 0.53	2.68 ± 0.56	0.094[b]
Hb	6.67 ± 1.94	7.39 ± 1.82	0.007*[a]
WBCs x 1000	3.15 ± 1.07	3.57 ± 2.96	0.791[b]
Plt x 1000	41.97 ± 61.88	48.45 ± 46.63	< 0.0001*[b]

FA: Fanconi anemia, n: sample size, SD: standard deviation, HC: head circumference, RBCs: red blood cells, Hb: hemoglobin, WBCs: white blood cells, Plt: platelets, *statistically significant *p-value ≤ 0.05*.
[a]: independent student T-test, [b]: Mann Whitney test.

Table 4: Comparing the degree of severity of aplastic anemia and frequency of blood transfusion in Non-FA and FA groups

		Non-FA group No. (% within variable)	FA group No. (% within variable)	*P-value*
Degree of severity of aplastic anemia	Non-severe	2 (28.6)	5 (71.4)	0.02*
	Severe	73(45.6)	87 (54.4)	
	Very severe	25(69.4)	11 (30.6)	
Frequency of blood transfusion	No	5 (55.6)	4 (44.4)	0.069
	Mild	15 (55.6)	12 (44.4)	
	Moderate	4 (21.1)	15 (78.9)	
	severe	76 (51.4)	72 (48.6)	

FA: Fanconi anemia, *statistically significant *p-value ≤ 0.05*

Table 5: Comparing age, percentiles and hematological parameters in DEB +ve group with one cell line and two cell lines

	FA with one cell line (n=90) Mean ± SD	FA with two cell lines (n=13) Mean ± SD	*P-value*
Age in years	9 ± 5	8.5 ± 2.5	0.739 [a]
Weight	24.73 ± 11.92	21.67 ± 6.04	0.155 [a]
Height	118.37 ± 22.05	118.65 ± 12.17	0.964 [a]
HC	48.78 ± 3.06	48.89 ± 2.60	0.911 [a]
RBCs x 1000000	2.65 ± 0.56	2.83 ± 0.57	0.294 [a]
Hb	7.35 ± 1.82	7.60 ± 1.92	0.652 [a]
WBCs x 1000	3.57 ± 3.14	3.55 ± 1.19	0.287 [b]
Plt x 1000	49.16 ± 49.17	43.53 ± 22.74	0.687 [a]

FA: Fanconi anemia, n: sample size, SD: standard deviation, HC: head circumference, RBCs: red blood cells, WBCs: white blood cells, Plt: platelets. [a]: independent student T-test, [b]: Mann Whitney test

Table 6: Comparing the degree of severity of aplastic anemia and frequency of blood transfusion in FA with one cell line and two cell lines

		FA with one cell line (n=90) No. (% within variable)	FA with two cell lines (n=13) No. (%within variable)	*P-value*
Degree of severity of aplastic anemia	Non-severe	5 (100)	0 (0)	0.100
	Severe	75 (86.2)	12 (13.8)	
	Very severe	10 (90.9)	1 (9.1)	
Frequency of blood transfusion	No	2 (50)	2 (50)	0.058
	Mild	10 (83.3)	2 (16.7)	
	Moderate	15 (100)	0 (0)	
	Severe	63 (87.5)	9 (12.5)	

FA: Fanconi anemia, n: sample size, *statistically significant *p-value ≤ 0.05*

DISCUSSION

Fanconi anemia (FA) is the most common inherited bone marrow failure syndrome. Patients with FA are usually suffering from pancytopenia, multiple organ affection and increased cancer risk. This study was conducted on a large group of 204 Egyptian patients suffering from congenital aplastic anemia. All patients were investigated using induction of breakage by 1,3-Butadiene diepoxide (DEB) to confirm the diagnosis of FA and according to the result of the DEB test patients were divided into two groups: 101 non-FA patients (with negative DEB test, Group 1) and 103 FA patients (with positive DEB test, Group 2).

This study was the largest Egyptian study conducted on 204 patients, in comparison to the previous Egyptian studies done by **Temtamy *et al.* *(2007)*** which included 48 patients and **El Bassyouni *et al.* *(2015)*** which included 32 patients.

The prevalence of FA in the present study was found to be high (50.5%) in total aplastic anemia patients which was in line with a previous Egyptian study reporting 34 FA out of 48 congenital aplastic anemia patients with a ratio of 70.8% (**Temtamy *et al.*, 2007**). This was in contrast to other studies which reported 33.7%, 16.6% and 13.1% (**Oostra *et al.*, 2012; Chowdhry *et al.*, 2014; Siddiqui *et al.*, 2020**) respectively. This data may reveal the high incidence of Fanconi anemia in our population compared to other ethnic groups, who were subjected to the same analysis.

The mean age group of non-FA anemia (group 1) and FA patients (group 2) was in accordance with other reports from the literature where most patients fall under the same age group (**Tipping *et al.*, 2001; Issaragrisil *et al.*, 2006; Alter Giri, 2016; Siddiqui *et al.*, 2020; Thompson *et al.*, 2021**).

The rate of consanguinity in this study was as high as 72.5%, which was also reported by **Siddiqui *et al. (2020)*** as 73%, while it was much lower in patients studied by **Korgaonkar *et al. (2010)* and Tamary *et al. (2010)***, who reported the rate of consanguinity as 36.4% and 40% respectively. The rate of consanguinity was also very low (1.3%) in an earlier study conducted on the French population (**Baumelou *et al.*, 1993**). These data may support the role of ethnicity, high consanguinity and endogamy in congenital aplastic anemia inheritance.

Also higher rate of consanguinity and higher ratio of affected family members were observed in group 2 of FA patients in comparison to group 1 non-FA patients. A similar study conducted on a large cohort of congenital aplastic anemia on the Tunisian population reported a significantly high frequency of consanguinity among FA as compared to non-FA patients, (93% and 43%, respectively), (**Talmoudi *et al.*, 2013**). This was also consistent with studies conducted by **Altay *et al.* (1997); Kesici *et al.* (2019)** and **Siddiqui *et al.* (2020)**, who reported a high frequency of consanguinity among FA patients of 78% 72.6%, and 94.2%, respectively. These data confirm the role of consanguinity in increasing the ratio of affected family members and the inheritance of Fanconi anemia.

In this study, gender had no significant difference between the two groups, but male predominance was observed in both non-FA and FA groups with a male to female ratio of 1.7:1 and 1.3:1, respectively. Male predominance was also observed in several previous studies (**Kutler *et al.*, 2003; Talmoudi *et al.*, 2013; Fiesco-Roa *et al.*, 2019; Kesici *et al.* 2019; Siddiqui *et al.*, 2020, Thompson *et al.*, 2021**) and was also observed in previous Egyptian studies done by **Temtamy *et al. (2007)*** and **El-Bassyouni *et al. (2015)***, who reported male to female ratios 1.3:1 and 1.8:1, respectively.

In our study, different percentages were observed for the most frequent first presentation which in non-FA patients (group 1) was growth retardation (29.7%), microcephaly (27.7%) and short stature (21.7%), while in FA patients (group 2) was growth retardation (52.4%), microcephaly (53.3%) and short stature (36.8%). Previous studies reported the same three presentations with different percentages; **Altay *et al.* (1997)** reported that 52% of the FA

patients were presenting by growth retardation, while **Alter (2003)**, and **Kutler *et al.* (2003)** reported 11% and 16%, respectively. A study done by **El Bassyouni *et al.* (2015)** on Egyptian patients reported that 35.3% of the patients presented with growth retardation, while they had reported a ratio of microcephaly similar to our study (52.9%). Microcephaly was reported as the first presentation by **Altay *et al.* (1997) and Temtamy *et al.* (2007)** in 42% and 48% of FA patients and 31% and 14% of non-FA patients, respectively. Microcephaly was reported as an evident sign in FA patients in multiple studies with variable prevalence. The study performed by **Kesici *et al.* (2019)** reported the highest rate of 92.6%. **While Alter (2003)**; **Kutler *et al.* (2003)**; **El Bassyouni *et al.* (2015), and Kesici *et al.* (2019)** reported rates of 51%, 63%, 64.7% and 75.4%, respectively. These rates of microcephaly were found to also higher than reported in this study. Short stature as the first presentation was reported also by **Temtamy *et al.* (2007)**, who recorded 52% for the FA group and 36% for the non-FA group which were higher than this study.

In the current study, all abnormalities including ophthalmological, nose, ear, upper limb, lower limb, skin, renal, cardiac, gastrointestinal, genital abnormalities were recorded in a significant higher percentage among group 2 patients (FA group) in comparison to group 1 patients (non-FA group).

Skin findings are common features in FA disease. In our study skin pigmentation was more prevalent in the FA group (42.7%) than the non-FA group (2.9%). **Temtamy *et al. (2007)*** reported similar results (52% in the FA group and 7% in the non-FA group). Also, skin findings were more prevalent in FA patients in other studies done by **Altay *et al. (1997)* and Kesici *et al. (2019)*** reporting ratios of 80% and 88% respectively.

Limb anomalies including radial and thumb anomalies were present in 52.4% of our FA patients but only 9.9% of non-FA patients had limb anomalies. These results were similar to **Kesici *et al*. (2019)** who recorded upper limb anomalies in 53.1% of FA patients, while different results were reported by **Temtamy *et al.* (2007)** and **El Bassyouni *et al.* (2015)**, who reported lower ratios of limb anomalies in FA patients (22.5% and 35.3% respectively). **Temtamy *et al.* (2007)** had detected a ratio of 28% of limb anomalies in the non-FA group.

In the current study, 17.4% of FA patients had renal anomalies which is not in accordance with **Temtamy *et al.* (2007)**, who reported a rate of 8% and **El Bassyouni *et al.* (2015) and Kesici *et al.* (2019)**, who reported a rate 29.4% and 30.9%, respectively. The present study reported eye abnormalities in 43.6% of FA group, which is different from the rates reported in previous studies. **Temtamy *et al.* (2007)** reported eye affection in 19% of their patients, while **Kesici *et al.* (2019)** reported a rate of 74.3%. Male genital abnormalities were also detected in this study, as well as in previous studies (**Fiesco-Roa *et al.*, 2019; Kesici *et al.* 2019**).

Uncommon abnormal EEG findings were observed in only 1% of patients in both groups. However, Danhofer and colleagues (2019) recorded abnormal EEG findings among their patients having hematological malignancies and aplastic anemia. An earlier study linked low voltage EEG and benign neonatal convulsions to FA (**Steinlein *et al.*, 1992**).

It is worthy to mention that the ratio differences in clinical findings and abnormalities between the current study and the previous two Egyptian studies done by **Temtamy *et al.* (*2007)* and El Bassyouni *et al.* (*2015)*** could be attributed to the smaller sample size.

Fanconi anemia patients are highly sensitive to DNA cross-linking agents like DEB and mitomycin C (MMC) (**Auerbach, 2009**). In our study, patients were tested for DEB sensitivity in lymphocyte cultures. All patients exhibited significantly elevated levels of chromosomal breakage compared to the non-FA group of patients. **Pinto *et al.* (2009)** had recommended the use of chromosomal breakage test as a FA screening test for all patients with BMF syndromes. Early diagnosis is important for genetic counseling and the choice of appropriate treatment when considering bone marrow transplantation for FA and immunosuppressive therapy for other causes of congenital aplastic anemia.

In this study there was no significant difference between mosaic and non-mosiac FA patients' percentiles, laboratory findings and clinical severity. This was in accordance with other studies reporting no difference between mosaic and non-mosiac FA patients (**Talmoudi *et al.*, 2013; Fargo *et al.*, 2014**). Nonetheless, it is important to identify mosaicism in FA patients planning for therapeutic stem cell transplantation. The presence of non-FA cells among FA hematopoietic cells is considered a risk factor for the success of engraftment as cross-linking agents-resistant T-cells might increase the risk of graft rejection (**Yabe *et al.*, 2012**).

Bone marrow failure is a major problem and could be the presenting feature in patients with congenital aplastic anemia including FA. In the current study the majority of patients exhibited severe aplastic anemia followed by very severe aplastic anemia and the least of patients had non-severe aplastic anemia with statistical significance between the non-FA and FA groups ($p=0.02$). These results were consistent with previous studies done by **Wali *et al. (2011)* and Chowdhry *et al.* (*2014)***. Similarly, in the study conducted by **Siddiqui *et al.* (*2020)***, the majority of their cohort had severe aplastic anemia (60.6%) while very severe aplastic anemia was present

in 25% of patients, however they recorded lower ratios in the FA patients (51.4%). On the other hand, **Goswami *et al*. (*2009)*** reported in their cohort a higher ratio of non-severe aplastic anemia (57.14%), than severe aplastic anemia (33.33%). This contradiction to our results could be owed to the financial burden of our medical service and lack of insurance plans. Also, in our community patients are usually seeking medical advice very late, making it difficult to be diagnosed in their milder conditions.

CONCLUSION AND RECOMMENDATIONS

This is the first study conducted on a large number of Egyptian patients suffering from congenital bone marrow failure syndromes. Fanconi anemia represents one of the high incidence diseases among BMFS in Egypt, which is in part explained by the high consanguinity and endogamy in our country. Our patients exhibited severe disease phenotype with affection of almost all the body organs. Accurate diagnosis is crucial for family counseling and management plans. As patients with FA will not respond to immunosuppressive therapy but could benefit from bone marrow transplantation, prevention and early detection of cancer among those patients is a must, in order to reduce the morbidity, mortality, and financial burden on the affected families and their reflection on the Egyptian society. Raising community awareness for Fanconi anemia as a disease and its high incidence among consanguineous parents should be also addressed. Wide molecular studies to identify the dominant FA types in the Egyptian population are highly recommended.

CONFLICT OF INTEREST

There are no conflicts of interest.

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