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Original

Fanconi anemia: A single center experience of a large cohort

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Fanconi anemia (FA) is an inherited disease, characterized by congenital malformations, short stature, progressive bone marrow failure and predisposition to leukemia and solid tumors. The aim of this study was to evaluate the clinical and prognostic features of FA patients followed in a single center.

The charts of FA patients were reviewed 35 years retrospectively and a total of 175 patients were included in the study in which 51.4% of patients were male. The mean age at diagnosis was 6.3±4.1 years. The incidence of microcephaly was 92.6%, skin findings were 88.0%, eye abnormality was 74.3%, thumb and radius abnormality was 53.1%, urinary system abnormality was 30.9%, skeletal system abnormality other than thumb and radius was 18.9%, genital system abnormality was 11.4%, cardiovascular system abnormality was 11.4%, ear and hearing abnormalities were 9.7% and gastrointestinal system abnormality was 5.7%. Short stature was present in 75.4% of the patients. Of the 175 patients 167 (95.4%) developed bone marrow failure during follow-up and the mean age of bone marrow failure was 7.1 ±3.7 years (1 month-old-19.8 years). The first clinical symptom was thrombocytopenia in 83.4% of patients. Malignancy developed in a total of 23 (13.1 %) patients (20 leukemia, 3 solid tumors) during follow-up. Of 175 patients, 35 (20%) underwent hematopoietic stem cell transplantation. Fatality rate among patients who underwent hematopoietic stem cell transplantation was 31.4% (11/35) and fatality rate among other patients was 63.4% (83/131; $p<0.05$). Of 94 patients who deceased, death was due to bleeding in 44.7%, infection in 34%, leukemia progression in 16.0% and graft versus host disease in 5.3%.

In terms of the number of patients included, this study is one of the largest cohorts with a remarkable duration of follow-up time. Hematopoietic stem cell transplantation was found to have a good impact on survival of patients.

Key words: Fanconi anemia, hematopoietic stem cell transplantation, congenital anomalies, leukemia, mortality.

Fanconi anemia (FA) is characterized with progressive bone marrow failure, congenital anomalies and predisposition to leukemia and other cancers and was firstly described by Guido Fanconi in three brothers in 1927.[1]

FA has an estimated incidence of 1 case per 100,000 live births, a prevalence estimated at 1 to 5 per million with a carrier frequency of approximately 1 in 300.[2] Incidence is slightly higher in males (M/F 1.2/1).[3] FA is reported in all races and ethnic groups but its prevalence is highest in Spanish travellers (1/70).[4] Until today at least 22 genetic subtypes have been defined in FA.[5] Most of the patients belong to FANCA, FANCC and FANCG.

Presence of physical anomalies is one of the cardinal findings of FA and 75% of individuals with FA have at least one physical anomaly. In FA patients skin findings (55-70%), skeletal anomalies (63-71%), eye anomalies (23-38%), ear and hearing anomalies (9-11%), gastrointestinal system anomalies (5-14%), urinary system anomalies (21-34%), genital system anomalies (20-32%), cardiopulmonary system anomalies (6-13%) are most encountered physical anomalies.[6,7] Physical anomalies commonly seen in FA patients were summarized in Table I.[6,7]

According to International Fanconi Anemia Registry (IFAR) data endocrine anomaly was detected in 81% of FA patients.[8] In a cohort of FA patients enrolled in the National Cancer Institute's inherited bone marrow failure syndrome study endocrine abnormality was reported in 73% of the patients.[9]

Increased susceptibility of FA cells to cross-linking agents was found to be very reliable for diagnosis. Although susceptibility of FA cells was studied for multiple agents diepoxybutane (DEB) and mitomycin C have been the commonly used agents.[10,11] Three to ten fold increased chromosomal breakage in DEB exposed lymphocytes compared to control group is diagnostic for FA.[12] These tests are highly sensitive and specific and also these tests allow diagnosis of patients before appearence of clinical findings and prenatal diagnosis.

The aim of this study was to evaluate the clinical and prognostic features of Fanconi anemia patients followed in a single center.

Material and Methods

The charts of FA patients and the charts of the patients who were ordered DEB induced

Table I. Physical Anomalies in Fanconi Anemia Patients.

Abnormalities	Study	
	Alter (N: 1.206)	IFAR (N: 754)
Low birth weight	11%	-
Growth retardation	11%	16%
Short stature	51%	63%
Skin findings	55%	64%
Skeletal anomalies	71%	-
Upper extremity anomalies	43%	49%
Genital system anomaly (male)	32%	20%
Genital system anomaly (female)	3%	-
Head anomaly	26%	-
Central nervous system anomaly	-	8%
Eye anomaly	23%	38%
Urinary system anomaly	21%	34%
Ear and hearing anomaly	9%	11%
Lower extremity anomaly	8%	-
Cardiopulmonary system anomaly	6%	13%
Gastrointestinal system anomaly	5%	14%
No anomaly	25%	30%
Only skin findings and/or short stature	11%	-

Alter: (Reference 6)
IFAR: International Fanconi Anemia Registry (Reference 7)

chromosomal breakage assay were reviewed 35 years retrospectively. Anemia was defined as hemoglobin (Hb) <10 g/dl, thrombocytopenia as thrombocyte count <100,000/mm^3 and neutropenia as absolute neutrophil count <1,000 mm^3.[7] Short stature was defined as height 2 standard deviations or more below the mean for children of that sex and chronologic age.

Androgen treatment was started when Hb level decreased below 8 g/dl or thrombocyte count decreased below 30.000/mm^3. Oxymetholone was used as androgen and started with the dose of 1-2 mg/kg and after the stabilization of hematologic findings, it was tapered off. Patients under androgen treatment were followed with hepatic ultrasonography and liver enzymes due to hepatic toxicity. Androgen treatment was discontinued if there was no improvement in hematologic findings in 6 months, in the case of side effects other than virilisation and also at least three months before hematopoietic stem cell transplantation (HSCT).

Severe bone marrow failure, need for red cell or platelet transfusion (Hb <8g/dl, thrombocyte count <20,000/mm^3), progression to myelodysplastic syndrome cytogenetically or morphologically, development of acute myeloid leukemia (AML) were indicators for HSCT in our center.

In our center cyclophosphamide and total body irradiation was used for preparation regimen for HSCT until 2004; and after this year fludarabine based regimen has started to be used.[13] HSCT complications seen in the first 100 days were defined as early complications and complications after this day were defined as late complications.

Institutional Ethics Committee approved the study. Data were analyzed using the SPSS version 21 program (Statistical Package for Social Sciences v.21, IBM, Chicago, IL). As descriptive statistics, number and the percentage of the patients were given. Pearson's Chi-square test and Fisher's exact test were, where appropriate, used to investigate the association between categorical variables. Two-sided p values <0.05 were considered statistically significant.

Results

Demographic findings

A total of 175 patients were included in the study. Ninety (51.4%) patients were male and male (M) to female (F) ratio of 1.1/1. Mean age at diagnosis was 6.3±4.1 years (1 month-19.8 years).

Major complaints at the time of diagnosis was bone marrow failure findings (paleness, bleeding, petechiae) in 105 (60.0%) patients, growth retardation in 29 patients (16.6%), family screening for FA in 17 patients (9.7%), physical anomaly in 15 patients (8.6%), leukemia in 4 patients (2.3%), renal failure in one patient (0.6%), stuttering in one patient (0.6%), hearing loss in one patient (0.6%) and cancer (Wilm's tumor) in one patient (0.6%).

The patient presented with renal failure had urogenital anomaly and diagnosed as FA because of accompanying thrombocytopenia and typical physical anomalies. The patient presented with stuttering directed to our department from pediatrics outpatient clinic because typical physical anomalies and growth retardation and DEB test confirmed diagnosis before the development of any abnormal hematologic finding.

There was consanguinity between parents of 127 (72.6%) patients. Cancer history was present in family history of 20 (11.4%) patients. There were siblings with FA history in 69 (39.4%) patients. Malignancies in non-FA relatives (20 patients) were leukemia in 10 (50%), head-neck cancer in 4 (20%), lung cancer in 2 (10%), stomach cancer in 2 (10%) and colon and prostate cancer in one patient.

Clinical and laboratory findings at diagnosis

DEB test was performed on 161 patients. In 144 (82.3%) patients DEB test was positive and in 17 (9.7%) patients the test was negative. DEB negative patients were diagnosed as FA because of typical physical anomalies, laboratory findings and classical clinic presentation and progression of FA.

Complementation group analysis was performed on 23 patients from 16 families. There were 18 patients in group FA-A (78.2%),

2 in group FA-G (8.7%), one in each group of FA-C (4.3%), FA-D2 (4.3%) and FA-E (4.3%).

Physical anomalies seen in our patients can be seen in Table II. Also physical anomalies that are detected in our case series and which are not common in patients with FA is shown in Table III.

There was an abnormal hematologic finding in 132 (75.4%) of the patients at the time of diagnosis. Mean presentation time of abnormal hematologic findings was 7.1±3.7 years (range: 1 month 19.8 years). At the time of data collection there was no abnormal hematologic finding in 8 patients and the oldest being 18 years old. There were no statistically significant difference between males and females for mean presentation time of an abnormal hematologic findings (M: 7.1±3.8 years, F: 7.2±3.6 years).

Complications during follow-up

Pancytopenia developed in 145 (%82.9) patients during follow-up. Malignancy developed in a total of 23 (13.1%) patients (20 leukemia, 3 solid tumors). In 8 patients (4.6%) with median ages at last visit were 7.6±5.9 (1.8-17 years) years, bone marrow was normal at the time of the study. For patients with leukemia, 19 had AML and 1 had ALL; mean age for leukemia development was 10.3 years (1.5-25 years).

Among the patients who had hematologic finding at diagnosis or developed cytopenia during follow up, initial finding was thrombocytopenia in 146 (83.4%) patients, anemia in 20 (11.4%) patients and neutropenia in one (0.6%) patient. Pancytopenia was present in 69 (39.4%) patients at the time of diagnosis.

Table II. Physical Anomalies in Fanconi Anemia Patients in Our Center (N: 175).

Physical Anomalies	N (%)
Skin findings	154 (88.0%)
Hyperpigmentation	120 (68.6%)
Hypopigmented spots	89 (50.9%)
Café-au-lait spot	139 (79.4%)
Thumb and radius	93 (53.1%)
Thumb	93 (53.1%)
Radius	10 (5.7%)
Skeletal system (other than upper extremity)	33 (18.9%)
Urinary system anomaly	54 (30.9%)
Genital system anomaly	20 (11.4%)
Female	2/85 (2.4%)
Male	18/90 (20%)
Gastrointestinal system anomaly	10 (5.7%)
Cardiopulmonary system anomaly	20 (11.4%)
Ear and hearing anomaly	17 (9.7%)
Eye anomaly	130 (74.3%)
Microcephaly	162 (92.6%)
Low birth weight (≤2500gr)	84 (48.0%)
Short stature	132 (75.4%)
Only skin and/or eye and/or growth retardation	41 (23.4%)

Table III. Physical Anomalies in Fanconi Anemia Patients in Our Center (N: 175).

System	Anomaly
Extremity	Cleft palate Pectus carinatum 11 ribs Winging scapula
Urinary system	Polycystic kidney
Genital system	Labial fusion
Gastrointestinal system	Diaphragmatic hernia Accessory spleen Mesenteric cyst
Cardiopulmonary system	Single atrium Aorticopulmonary collateral Bicuspid aorta Left persistent superior vena cava
Eye	Blepharophimosis

Mean age of the patients who had pancytopenia at diagnosis was 7.6±3.9 years and mean age of the patients who had cytopenia but not pancytopenia was 5.4±3.8 years and the difference between these two groups was statistically significant ($p<0.05$).

Solid tumor developed in 3 (1.7%) patients; glioblastoma multiforme in one patient; glioma in another patient; triple subsequent malignancies of Wilm's tumor, AML and medulloblastoma in another patient.

Short stature was present in 132 (75.4%) patients, Endocrinologic abnormality was evaluated in 141 (80.4%) patients; it revealed growth hormone deficiency in 3 (2.1%), hypothyroidism in 2 (1.4%), impaired glucose tolerance in 2 (1.4%) and osteoporosis in 2 (1.4%) of the patients. Two of the female patients got pregnant but had fetal loss. One of the male patients had a healthy baby during follow-up.

Treatments and survival

A total of 53 (30.3%) of the 175 patients were put on androgen treatment and 69 side effects were seen in these patients. These side effects were virilisation in 38, liver toxicity (hypertransaminasemia) in 15, galactorrhea in 7, peliosis hepatis in 5, hepatic adenoma in 3 and hypertension in one patient. In case of side effects other than virilisation, androgen treatment was stopped and all of these side effects other than hepatic adenoma were reversible.

Surgical operations for physical anomalies were applied to 17 (9.7%) of the patients. These anomalies were limb anomaly in 6 (35.3%), genitourinary system anomaly in 5 (29.4%), gastrointestinal anomaly in 4 (23.5%) and eye anomaly in one (5.9%) patient and both extremity and genitourinary system anomaly in one patient. Sixteen of the patients (16/17, 94.1%) who needed surgical operation for anomalies underwent surgery before the onset of bone marrow failure.

Thirty five patients (20.0%) had undergone HSCT. The indications for HSCT were AML in three (8.6%) patients and severe bone marrow failure in 32 (91.4%) patients. Mean age at HSCT was 11.6±5.6 years (5.5-31.6 years). Donors were relatives in 30 (85.7%) patients and unrelated subjects in 5 (14.3%) patients. Related donors were human leukocyte antigen (HLA)-identical and DEB negative sibling in 21 patients, HLA-identical other relatives in six patients, and HLA 1-antigen mismatched sibling in three patients.

Early HSCT complications developed in 23 (65.7%) of the patients. These complications were organ toxicity (n: 9), graft-versus-host disease (GvHD) (n: 9), infectious complications (n: 5), engraftment failure (n: 2) and venoocclusive disease (n: 1). Late HSCT complications developed in 5 (14.3%) patients and these were chronic GvHD in four patients and secondary ALL in one patient.

Twenty four patients who had undergone HSCT were alive and mortality rate among the HSCT patients was 31.4% (11/35) at the time of the study. Mortality rate of the other patients who had not undergone HSCT was 63.4% (83/131) and the difference between these two groups was statistically significant ($p<0.05$).

Among the patients who had undergone HSCT, 12 of them had undergone HSCT in outer centers and 23 of them in our center. In our center fludarabine based preparation regimen has started to be used after 2004. Mortality rate of the patients who had undergone HSCT before and after 2004 was 62.5% (5/8) and

20% (3/15), respectively. Difference between these two groups was statistically significant ($p<0.05$).

At the time of the study 72 (72/166; 43.4%) patients were alive and 9 patients were lost to follow-up.

Cause of death was bleeding in 42 (44.7%), sepsis in 32 (34.0%), AML in 14 (14.9%) , GvHD in 5 (5.3%) and ALL in one (1.1%) patient. Mean survival time was 11.6 years (2-31.6 years). Mortality rate of the patients who had pancytopenia at diagnosis or not was 81% and 40%, respectively and this difference was statistically significant ($p<0.05$).

Discussion

Our study is one of the largest cohort studies reporting characteristics of FA patients. FA is seen slightly more frequently in male subjects. In our study male/female ratio was 1.1/1 and this ratio is consistent with previous studies.[7] Also it was found that gender had no effect on age of diagnosis, age of hematologic finding occurrence, number of physical anomalies, survival rate and mean life span.

One of the major findings of FA is bone marrow failure developing in 80% of the patients and is the major presenting feature.[7] In our series 60% of the patients were diagnosed during the bone marrow failure work-up. The other findings at presentation were growth retardation, family screening, malformation, leukemia, renal failure, stuttering, strabismus, hearing loss and cancer in our cohort. Renal failure and stuttering have not been reported as presentation findings for FA previously.

Mean occurrence time of hematologic finding was found as 7.1 years and consistent with previous two case series.[7] It is known that first cytopenia that develops in FA is thrombocytopenia.[14] Parallel to this knowledge thrombocytopenia is leading cytopenia in 83.4% of our patients.

Mean age of the patients who had pancytopenia at diagnosis was 7.6 years and mean age of the patients who had cytopenia but not pancytopenia was 5.4 years. This finding confirms that disease begins with cytopenia and progresses to pancytopenia. At the time of data collection fatality rate of the patients who had pancytopenia at diagnosis and those who did not were 81% and 40%, respectively ($p <0.05$). According to our data presence of pancytopenia at diagnosis is a poor prognostic indicator.

FA-A is the most common complementation group and covers 65% of patients.[15] Consistent with this report FA-A is the most common complementation group (78.2%) in our study. Frequency of other groups were consistent with previous studies.

Endocrinologic abnormality was present in 80.4% of the patients and this ratio was 73% and 81% IFAR and National Cancer Institute's study, respectively.[9,16] Short stature is also common in FA patients and is seen in 75.4 of our patients. In Alter's and IFAR case series short stature was present in 51% and 63% of the patients, respectively.[6,7] Endocrinologic abnormalities are not rare in FA patients and it is important to be aware of these abnormalities and patients should be screened for endocrine abnormalities at diagnosis and during follow-up.

During follow up abnormal hematologic findings were seen in 95.4% (167/175) of the patients. Progression to pancytopenia occurred in 83%, leukemia in 11.4% and solid tumor in 1.7%. In IFAR case series bone marrow failure was seen in 80% of 754 patients.[7] In same series malignancy was reported in 23% of the patients and among malignancies 60% of them were leukemia and 40% of them were solid tumor. When compared with IFAR case series, solid tumor development is rare in our case series. This could be secondary to the fact that patients had died before they reached the age for increased cancer risk.

In this study among the patients who developed leukemia, the type of leukemia was AML in 19 patients and ALL in one patient. In IFAR series leukemia was AML in 50%, MDS in 44%, ALL in 4%, CML in 0.8% and lymphoma in 0.8%.[7] In four patients leukemia was the presenting cause as reported before.[17] AML prognosis is poor in FA patients and it is known that most patients die within 6 months of an AML diagnosis.[14] In our series 18 of AML

patients including three who received HSCT died in mean 6.9 months. In light of these findings it could be emphasized that screening for FA in AML patients and close follow up for development of AML after FA diagnosis is important.

Three patients had solid tumors (Wilm's tumor, medulloblastoma, glioblastoma multiforme and glioma). In previous case series the most common solid tumor in FA patients was squamous cell carcinoma localized to head and neck region.[7,18,19]

HSCT was applied to 20% of the patients. In IFAR series HSCT was applied to 36% of the patients. Survival rate of patients in which HSCT was better, compared to others. This finding shows that HSCT is the only curative treatment for FA.

In our study we found that fatality rate of HSCT applied patients decreased from 62.5% to 20% after the use of fludarabine based preparation regimen. HSCT is a unique curative treatment for FA but it is important to use less toxic regimens, regimens without total body irradiation are especially important.

FA is most commonly an inherited bone marrow failure in our country. Screening for diagnosis, proper test choice for diagnosis, detailed work up for physical anomalies and hematologic findings during diagnosis, close follow up for bone marrow failure and malignancy development after diagnosis, adequate supportive treatment after bone marrow failure and application of HSCT is important for FA patients. In terms of the number of the patients included, this study is one of the largest studies in the literature; and it revealed important clinical and laboratory findings of Fanconi anemia patients.

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