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CLINICAL PROFILE OF FANCONI ANEMIA IN A TERTIARY CARE CENTRE

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ABSTRACT

Background: Fanconi Anemia (FA) is a rare genetic disorder characterized by DNA repair defects, bone marrow failure, and physical anomalies. This study describes the clinical and spectrum of FA in pediatric patients. Early diagnosis of Fanconi anemia can help in appropriate and timely management **Methods:** A retrospective study of 15 children diagnosed with FA via chromosomal breakage and/or mutation studies was conducted over four years. Data on clinical history, physical anomalies, hematological status, and genetic findings were recorded. **Results:** The mean age at presentation was 5.4 ± 1.7 years, with a male: female ratio being 0.875:1. Consanguinity was present in 60% of cases. Bleeding (53.3%) and fever with anemia (46.7%) were the most common symptoms, though 20% were asymptomatic at diagnosis and were detected on family screening. Pancytopenia was present in 80% of patients. Physical anomalies were found in all patients, most commonly typical facies (80%), short stature (53.3%), and limb anomalies (33.3%). Chromosomal breakage studies were positive in 93% of patients. FANCA (33.3%) and FANCG (26.6%) were the primary genetic mutations identified. Out of 15 patients, 3 (20 %) underwent successful hematopoietic stem cell transplant (HSCT), while one patient is being worked up for HSCT. 3 (20%) expired (1 AML, 1 IC bleed & 1 of sepsis), & 1 patient was lost to F/U. 7 patients are on decadurobolin with prednisolone and on regular follow up. **Conclusion:** Due to phenotypic heterogeneity, FA diagnosis requires high clinical suspicion and confirmation via cytogenetic or molecular testing. Early identification, including sibling screening, is vital for timely hematopoietic stem cell transplantation.

INTRODUCTION

Fanconi anemia (FA) is a rare genetic disorder, due to a defect in the deoxyribonucleic acid (DNA) repair pathway, resulting in congenital abnormalities and decrease in all three blood cell lines. It is the most common cause of inherited bone marrow failure characterized by pancytopenia and increased susceptibility to cancers. It can affect almost all organs of the body. (1) The disease is inherited in an autosomal-recessive manner, but an X-linked form has also been described. (2) FA is genetically and phenotypically heterogeneous owing to mutations associated with at least 22 different genes (2)

The FA cells have hypersensitivity to alkylating agents due to a defect in DNA repair genes. The diagnosis can be established by genetic studies or cytogenetic analysis of lymphocytes with Diepoxybutane (DEB) or mitomycin C (MMC), which shows increased chromosomal breakage in Fanconi anaemia.

The clinical phenotype is extremely variable; therefore, diagnosis is delayed until pancytopenia appears. Besides an early onset of anemia in childhood, patients may present extra-hematological physical signs and have an increased risk of malignancies (acute myeloid leukemia and solid tumors). Thus, studies describing clinical spectrum of presentation may help in increase the awareness for early diagnosis.

Timely diagnosis can help plan an appropriate treatment of FA with bone marrow failure with hematopoietic stem cell transplantation (HSCT), which is different from treatment of acquired bone marrow failure.

Methods & Materials

It was a retrospective observational study, including 15 children of Fanconi anemia diagnosed on chromosomal breakage study and/or mutation study, who presented to division of Pediatric Hematology Oncology, at our institute over last 4 years. Children <18years of age with hypoplastic anemia, bone marrow failure &/or dysmorphic features on examination were worked up to rule out Fanconi anemia. Chromosomal breakage was examined in short term cultures of peripheral blood Lymphocytes in the presence of Mitomycin C in a standardized laboratory. Patients with confirmed diagnosis of Fanconi anemia based on either chromosomal breakage study (MMC induced) and/or homozygous gene mutations were included in the study.

Detailed clinical history including presenting complaints, consanguinity, family history, age of presentation, and treatment details were noted. Pedigree analysis was done for each case & a thorough clinical examination was performed on these children. Baseline complete blood count and Hb F values (by high performance liquid chromatography) were recorded. Bone marrow aspirate & biopsy were noted, whenever performed. 2 d echo, skeletal survey, ophthalmologic evaluation and abdominal ultrasonography done to rule out associated anomalies were recorded.

RESULTS:

Total of 15 patients were included in the studies. The mean age at presentation was 5.4±1.7 years (Range 4-10 years). There were 7 males & 8 females in our study, with male to female ratio being 0.875: 1, stating female preponderance. Third degree consanguinity was present in 9 patients (60%). Bleeding (8 patients, 53.33%) was the most common presenting feature followed by fever with anemia (7 patients, 46.67%). Three (20%) patients were diagnosed on sibling screening of index cases and were asymptomatic at diagnosis. 12 (80 %) out of 15 patients had pancytopenia at presentation, 2 (13.3%) patients had only thrombocytopenia, 1 patient presented with leukemia. All patients had increased Hb F values.

All the patients had at least one physical anomaly, either skeletal anomaly or dysmorphic features. Twelve (80%)

patients had typical facies (triangular facies and mid-face hypoplasia). Short stature was present in 8 (53.3%) patients, limb anomaly was present in 5 (33.33%) patients (polydactyly and syndactyly in 2 patients each, hypoplastic thumb in 1 patient), microphthalmia in 4 (26.6%) patients. Dysmorphic features in our series are microcephaly, syndactyly, polydactyly, microphthalmia, conical teeth, undescended testis as described in table 1 & constitutes 12 (80%) patients. Renal anomaly was present in 3 (20%) patients. None had congenital heart disease. (table 1)

Chromosomal breakage studies were positive in all patients except one patient, (93% - positive)(p value < 0.001). Mutation studies were done in 9 patients. Most common FANC gene found in our study was FANC-A (n=5, 33.3%), followed by FANC-G (n=4,26.66%) gene.

Outcome: Out of 15 patients, 3 (20 %) underwent successful hematopoietic stem cell transplant (HSCT) with 100 % chimerism and no graft versus host disease on follow up, while one patient is being worked up for HSCT. 3 (20%) expired (1 AML, 1 IC bleed & 1 of sepsis), & 1 patient was lost to F/U. 7 patients are on decadurobolin with prednisolone and on regular follow up.

Table 1: Clinical features of Fanconi anemia

Clinical feature	Frequency (percentage)
Bleeding	8 (53.3%)
Fever	7 (46.7%)
Pancytopenia	12 (80%)
Thrombocytopenia	2 (13.3%)
Leukemia	1 (6.6%)
Short stature	8 (53.3)
Microphthalmia	5(33.3)
syndactyly	2 (13.3)
Microcephaly	4 (26.6)
Polydactyly	2 (13.3)
Hypoplastic thumb	1(6.6)
Café au lait spots	2 (13.3)
Undescended testis	2(13.3)
Conical teeth	1(6.6)
Hypertelorism	1(6.6)

DISCUSSION

Fanconi anemia (FA) was first described in 1927 by Guido Fanconi, who observed three siblings presenting with multiple congenital abnormalities and aplastic anemia (2). FA is a rare inherited chromosomal instability syndrome caused by defects in DNA repair pathways and cell-cycle regulation (3,10,11). Most cases demonstrate an autosomal recessive pattern of inheritance and are characterized by progressive bone marrow failure, congenital malformations, and an increased predisposition to hematological and solid malignancies at an early age (3,14).

In our study, the age at diagnosis ranged from 4 to 10 years, with a mean age of 5.4 ± 1.7 years. This was younger than that reported by Butturini et al. and Kutler et al., who documented a median age at diagnosis of approximately 7 years (4,5). Earlier diagnosis in our cohort may be attributed to family screening, through which three asymptomatic children were identified before the onset of significant clinical manifestations.

Among the 15 patients included in the study, there were 7 males and 8 females, yielding a male-to-female ratio of 0.875:1 and suggesting a slight female predominance. Similar findings have been reported in a Brazilian cohort, where a modest female predominance was also observed (8). However, the literature remains inconsistent regarding sex distribution in FA, with some studies reporting equal prevalence and others demonstrating male predominance (19).

Consanguinity was present in 60% of patients in our study. Given the predominantly autosomal recessive inheritance pattern of FA, a high prevalence of parental consanguinity has been reported across multiple studies (1,8). A Moroccan study documented consanguinity in 55% of affected patients, supporting the role of consanguineous marriages in increasing disease occurrence (1).

All patients in our cohort exhibited at least one physical anomaly. Typical facies, characterized by triangular facies and mid-face hypoplasia, were observed in 80% of patients. Short stature was present in 53.3%, while limb anomalies were identified in 33.3%, including polydactyly, syndactyly, and hypoplastic thumb. These findings are consistent with previous reports. Korgaonkar et al., in a study of 33 Indian patients with FA, reported short stature in 81.8%, skin pigmentation abnormalities in 45.5%, and skeletal anomalies in 48.5% of patients (6).

Renal anomalies were detected in 20% of patients in our study. Renal abnormalities such as horseshoe kidney, ectopic kidney, renal hypoplasia, dysplasia, and hydronephrosis have been well documented in FA (14,22). Ophthalmological abnormalities were identified in 33.3% of patients, most commonly microphthalmia. These findings are comparable to those reported by Graf et al. in their large single-center study evaluating ocular manifestations in 106 patients with FA (13). Cutaneous manifestations were relatively uncommon in our cohort, with café-au-lait spots observed in 13.3% of patients. Previous studies have shown that petechiae, purpura, and generalized hyperpigmentation are more frequent dermatological findings, whereas café-au-lait macules occur less commonly (7).

Bone marrow failure remains the hallmark hematological manifestation of FA. In our study, 80% of patients presented with pancytopenia, while thrombocytopenia alone was observed in 13.3%. One patient presented with acute leukemia at diagnosis. Similar hematological abnormalities have been reported in studies from Brazil and Morocco (1,8). The chromosomal instability characteristic of FA results from defective DNA repair mechanisms, leading to accumulation of DNA damage, cellular senescence, bone marrow failure, myelodysplastic syndrome, and leukemic transformation (10,11,15,16).

Chromosomal breakage studies were positive in 93% of patients, confirming their diagnostic utility. Molecular analysis was performed in nine patients. FANCA mutations were the most common, identified in five patients (33.3%), followed by FANCG mutations in four patients (26.7%). Globally, pathogenic variants in FANCA account for approximately 60–70% of FA cases (14). Similar findings were reported in the Moroccan cohort, where FANCA mutations constituted two-thirds of all identified variants (1). Korgaonkar et al. also demonstrated significantly increased spontaneous and induced chromosomal breakage in Indian patients with FA, highlighting the importance of cytogenetic testing in diagnosis (6).

Without definitive treatment, FA is associated with progressive bone marrow failure and reduced life expectancy. The median survival of untreated patients has been reported to be approximately 20–30 years (9,17). Hematopoietic stem cell transplantation (HSCT) remains the only curative therapy for hematological manifestations of the disease (20).

In our cohort, three patients (20%) successfully underwent HSCT and achieved complete donor chimerism without evidence of graft-versus-host disease. One additional patient is currently undergoing transplant evaluation. Three patients died during follow-up due to acute myeloid leukemia, intracranial hemorrhage, and sepsis, respectively, while one patient was lost to follow-up.

Seven patients continue to receive androgen-based therapy with nandrolone decanoate and prednisolone and remain under regular follow-up. Notably, three of these patients were diagnosed through family screening and had only mild cytopenias at presentation. Previous studies have demonstrated that androgen therapy can improve hematopoiesis in selected FA patients, although long-term treatment is associated with adverse effects including virilization, hepatotoxicity, and an increased risk of hepatic tumors (17).

A retrospective study from India evaluating outcomes of allogeneic HSCT in FA reported overall survival and disease-free survival rates of 65% and 50%, respectively, with an overall mortality of 30% (21). These findings indicate that HSCT is a feasible and effective treatment option even in resource-limited settings, despite challenges related to delayed referral, transfusion burden, and recurrent infections.

CONCLUSION

Fanconi anemia is a rare inherited bone marrow failure syndrome characterized by marked phenotypic and genetic heterogeneity. Because of the wide spectrum of clinical manifestations, diagnosis cannot be based solely on clinical findings. Chromosomal breakage analysis remains an important diagnostic tool, while molecular testing is essential for confirming the diagnosis, identifying the underlying genetic defect, providing prognostic information, facilitating genetic counselling, and guiding therapeutic decisions.

Early recognition of clinical features, timely genetic diagnosis, family screening of at-risk relatives, and prompt referral for hematopoietic stem cell transplantation can significantly improve outcomes in patients with Fanconi anemia (20,21).

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