Original Article

Clinical profile of children with Fanconi anemia from a tertiary center in Southern India

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ABSTRACT

Objectives: The aim of this study is to observe the clinical spectrum of presentation of Fanconi anemia (FA) in children presenting to the Hematology Department of Victoria Hospital, Bangalore Medical College and Research Institute. **Materials and Methods:** This observational study was carried out from February 2010 to December 2016 on all the 16 consecutive children <18 years of age, with FA. Those with high frequency of chromosomal breakage in G-banded metaphases from mitomycin-treated cultures were considered as positive cases. **Results:** The mean age at presentation was 6.79±1.34 years, but for those with dysmorphic features on examination, it was 4.77±0.98 years. Symptoms of anemia were seen in 14 (87.5%) and of bleeding in 8 (50%) cases. There was a history of prolonged fever at presentation in 5 (31.2%) cases. Dysmorphic features on examination were seen in 10 (62.5%) cases. Short stature and microcephaly and microphthalmia were the most common features. Pancytopenia was seen in 68.7% of the subjects at presentation and anemia in 87.5% of cases while thrombocytopenia was universal (100%). The mean hemoglobin was 5.33±0.36 g/dL, mean white blood cell count was 3429.37±477.65/mm^3, and mean platelet count was 28156.25±4199.44/mm^3. The bone marrow was hypoplastic in 14 (87.5%). Pelvic kidney seen in 5 (31%) was the most common ultrasound finding. Parental consanguinity was seen in 50% of cases. **Conclusion:** Parental consanguinity was common, and there was a male preponderance in our study. The most common presenting manifestations were anemia followed by bleeding. Two-third of the patients had pancytopenia at diagnosis while thrombocytopenia was universal (100%). In the presence of a family history and/or dysmorphic features, even mono- or bi-cytopenias should be evaluated for inherited bone marrow failure syndromes.

Key words: *Children, Dysmorphic features, Fanconi anemia, Karnataka*

Fanconi anemia (FA) is an autosomal recessive chromosomal instability syndrome characterized by congenital abnormalities, progressive bone marrow failure, and cancer predisposition [1,2]. In 1927, Guido Fanconi first reported 3 brothers with pancytopenia and physical abnormalities. The current diagnostic test for FA consists of cytogenetic quantitation of chromosomal breakage in response to diepoxybutane (DEB) or mitomycin C (MMC). FA cells are sensitive to DNA cross-linking agents. Complementation analysis of FA cells using somatic cell fusion has facilitated the identification of thirteen complementation groups so far, suggesting that FA is a genetically heterogeneous disorder and sequentially named as FANC (subtypes A, B, C, D1, D2, E, F, G, I, J, L, M, N) [1-3]. The majority of affected children belong to FA Group A [1,2].

The male-to-female ratio in the literature cases is 1.2:1, although equal numbers are expected in autosomal recessive disease. FA has been diagnosed from birth to age 48 years, with a median age of 7-8 years. Individuals with birth defects are diagnosed at younger ages than persons without birth defects. Bone marrow failure usually presents in childhood, with petechia, bruising, and hemorrhages due to thrombocytopenia; pallor and fatigue from anemia; and infections due to neutropenia. More than 90% of the children with FA develop pancytopenia caused by aplastic anemia, which is often fatal [1-3].

About 75% of children with FA have birth defects, such as altered skin pigmentation and/or café au lait spots (>50%), short stature (50%), thumb or thumb and radial anomalies (40%), abnormal male gonads (30%), microcephaly (25%), eye anomalies (20%), structural renal defects (20%), low birth weight (10%), developmental delay (10%), and abnormal ears or hearing (10%). Literature reports may, however, be biased toward this association because the clinical diagnosis was initially dependent on the combination of aplastic anemia and physical anomalies; thus, the frequencies may be overestimated [1,2,4].

The clinical phenotype is extremely variable; therefore, the diagnosis is frequently delayed until the pancytopenia appears. Thus, studies like ours on the clinical spectrum of presentation increase the awareness and improve the chances of early diagnosis of this rare disease. Timely diagnosis helps plan the appropriate treatment of FA-associated bone marrow failure and stem cell transplantation (SCT) protocols, which are different from treatment of acquired bone marrow failure.

MATERIALS AND METHODS

This study included 16 consecutive children of FA who presented to the Hematology Department of Victoria Hospital, Bangalore Medical College and Research Institute, from February 2010 to December 2016. Children <18 years of age with hypoplastic anemia, bone marrow failure, and/or dysmorphic features on examination were worked up to rule out FA. Those with high frequency of chromosomal breakage in G-banded metaphases from mitomycin-treated cultures were considered as positive cases.

Detailed clinical history including family history, mode of presentation, age of onset of the disease, associated symptoms, and drug history were noted. Pedigree analysis was done for each case, and a thorough clinical examination was performed on these children <18 years of age. Informed written consent was obtained for the use of patient information for research and studies.

The blood sample was subjected to routine hematological tests such as complete blood count using automated hematology analyzer (5 part Beckman LH 780 analyzer for HB, HCT, TLC, differential leukocyte count, and platelet count), and peripheral smear examination was performed. Routine liver and kidney function tests were done in all. Bone marrow aspirate and biopsy and routine karyotyping were performed in all children. Chromosome breakage was examined in short-term cultures of peripheral blood lymphocytes in the presence of MMC. Fetal hemoglobin (HbF) was estimated by semi-automated gel electrophoresis. Skeletal survey was performed to identify all developmental defects involving bone. An initial abdominal ultrasound was performed to look for size and location of the kidney and any other anomalies.

RESULTS

The mean age at presentation was 6.79±1.34 years (Range: 2-18 years). The mean age at diagnosis of those with dysmorphic features on examination was 4.77±0.98 years. There were 12 males and 4 females. The M:F ratio was 3:1. There was a history of parental consanguinity in 8 (50%) cases Table 1. Symptoms of anemia were seen in 14 (87.5%) and symptoms of bleeding such as skin and mucosal bleeds, hematemesis and hemoptysis in 8 (50%). One child presented with leukemia. There was a history of prolonged fever at presentation in 5 (31.2%). Developmental delay was seen in 3 (18.6%). Dysmorphic features on examination were seen in 10 (62.5%) of the children as shown in Table 2. Dysmorphic features on examination seen in our series included short stature, microphthalmia, microcephaly, hypoplastic thumb, polydactyly, and hyper- and hypo-pigmentation (Table 2). Short stature and microcephaly and microphthalmia were the most common, followed by hyperpigmentation, hypoplastic thumb, and polydactyly.

Pancytopenia was seen in 68.7% of the subjects at presentation and anemia in 87.5% while thrombocytopenia was universal (100%)

Table 1: Clinical features at presentation

Clinical features	n (%)
Anemia	14 (87.5)
Bleeding	8 (50)
Fever	5 (31.2)
Leukemia	1 (6.2)
Developmental delay	3 (18.6)
Dysmorphic features	10 (62.5)
Hepatomegaly	7 (43.7)
Splenomegaly	3 (18.6)
Hepatosplenomegaly	3 (18.6)

Table 2: Dysmorphic features seen on examination

Feature	n (%)
Short stature	6 (60)
Microphthalmia	6 (60)
Microcephaly	6 (60)
Hypoplastic thumb	4 (40)
Polydactyly	4 (40)
Hyperpigmentation	4 (40)
Hypopigmentation	2 (20)
Café au lait spots	2 (20)
Anal agenesis	1 (10)
Undescended testes	2 (20)
Spinal dysraphism	2 (20)
Hearing defect	2 (20)

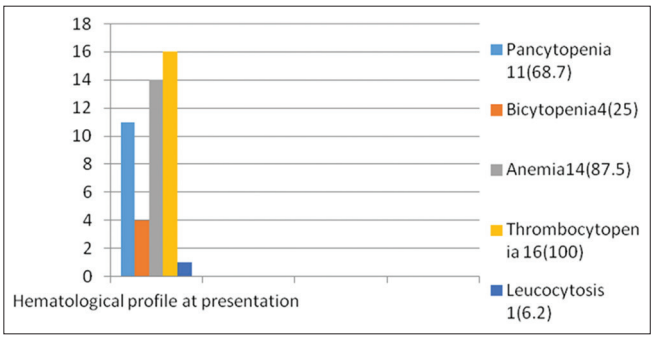

Figure 1: Hematological profile at presentation

(Fig. 1). The mean levels of hemoglobin was 5.33±0.36 g/dL, mean white blood cell count was 3429.37±477.65/mm^3, and mean platelet count was 28156.25±4199.44/mm^3. The bone marrow was hypoplastic in 14 (87.5%), hypercellular in 1 (6.2%), and showed features of acute myeloid leukemia in 1 (6.2%).

Routine karyotyping was normal in all 16 cases. Peripheral blood cytogenetics using G-banded metaphases from mitomycin-treated cultures showed a high frequency of chromosomal breakage in all (100%) patients. HbF was elevated in all. Pelvic kidney, seen in 5 (31%) cases, was the most common ultrasound finding, followed by ectopic kidneys in 3(18.6%) and absent kidneys in 2 (12.4%). Absent uterus was seen in 1 female child (6.2%). On skeletal survey, absent radius was seen in 3 (18.6%) and absence of carpal bones was seen in 2 (12.4%) cases.

DISCUSSION

Hypersensitivity of FA cells to the clastogenic effect of DEB or MMC provides a unique marker for the diagnosis before the beginning of hematological manifestations [3,5,6]. These agents lead to increased numbers of breaks, gaps, rearrangements, and quadriradii in FA homozygote cells. Bone marrow aspirate and biopsy may reveal hypocellularity, loss of myeloid and erythroid precursors and megakaryocytes (with relative lymphocytosis), or full-blown aplasia with a fatty marrow. HbF may be increased for age as a manifestation of stress erythropoiesis.

Treatment is recommended for significant cytopenias, such as Hb <8 g/dL, platelets <30,000/μL, or neutrophils <500/mm^3. Although the first line of therapy is SCT, androgens usually oxymetholone 2-5 mg/kg/day, to which approximately 50-75% of children respond, are used for those in whom transplantation is not an option [1,2,4]. These improvements may be only in Hb, or bi- or tri-lineage, and may be brief or last for many years. Severe neutropenia may respond to granulocyte colony-stimulating factor, and some children also demonstrate an increase in Hb and platelets with this treatment [1,2,4]. While gene therapy is tantalizing in FA, it is not yet a reality [7,8]. If there is a human leukocyte antigen-matched sibling, SCT is the recommended course.

Supportive care for children with symptomatic anemia includes transfusions of packed red blood cells that have been leukodepleted. Symptomatic thrombocytopenia can be treated with similarly treated platelets; single-donor platelets are preferred to reduce the frequency of antibody formation. Hand surgery and splinting may be indicated for thumb and radial anomalies which should be performed early in life to ensure maximal function. Congenital heart defects may require surgery. GI anomalies, such as tracheoesophageal fistulas, are also treated surgically. The major cause of death in FA is bone marrow failure, followed in frequency by leukemia and solid tumors [7-9]. The projected median survival from all causes for more than 1000 cases reported in the literature is age of 20 years, although this has improved to older than 30 years in the cases reported in the most recent decade [8,10].

In our study, parental consanguinity was seen in 50% of cases, highlighting the importance of community education, premarital counseling, and promotion of eugenics. The mean age at presentation was 6.79±1.34 years, but for those with dysmorphic features on examination, it was 4.77±0.98 years. Thus, those with dysmorphic features on examination were diagnosed earlier as also reported by other researchers [9,11,12]. The clinico-hematological findings were similar to studies reported previously. There was a male preponderance in our study. The most common presenting manifestations were anemia followed by bleeding similar to studies from Azik et al. [13] and Auerbach et al. [14]. Two-third of the patients had pancytopenia at diagnosis while thrombocytopenia was universal (100%).

Developmental delay was seen in 3 (18.6%) and dysmorphic features on examination was seen in 10 (62.5%) of the children. Short stature and microcephaly and microphthalmia were the most common anomaly, followed by hyperpigmentation, hypoplastic thumb, and polydactyly similar to the findings of other studies [11-17]. Zen PR et al (PR stands for Paulo Ricardo) [16] and Auerbach et al. [14] have reported similar findings. Radial abnormalities, a classic finding of FA, are described in about 50% of the children and mainly consist of absence or hypoplasia of the thumb, bifid or supernumerary thumbs, and absence or hypoplasia of the radius [9-11]. We found hypoplastic thumb in 40%, polydactyly in 40%, and absent radius was seen in 18.6% and absence of carpal bones was seen in 12.4% cases in our study population.

Pelvic kidney, seen in 5 (31%) cases, was the most common ultrasound finding. Among the genital anomalies detected, 2 (20%) males had undescended testes and 1 female had absent uterus. Around one-third of FA patients have been reported to have renal anomalies including unilateral renal aplasia, renal hypoplasia, horseshoe kidneys, or double ureters [11,12]. Males have a high incidence of genital abnormalities such as hypogenitalia, undescended testes, and hypospadias with infertility being the norm, although there have been reports of males with FA fathering children [11,12,18]. Females may also have underdeveloped genitalia and uterine anomalies; older females have sparse, irregular menses but can become pregnant if not on androgen therapy [11].

Although the study population was small, the numbers were reasonable for a single center and a rare disease. Larger and multicenter studies would be useful to throw more light on the clinical spectrum of FA in children.

CONCLUSION

Parental consanguinity was common in our study highlighting the importance of community and youth education, pre-marital counseling, and promotion of eugenics. There was a male preponderance in our study. The most common presenting manifestations were anemia followed by bleeding. Two-third of the patients had pancytopenia at diagnosis while thrombocytopenia was universal (100%). In the presence of a family history and/or dysmorphic features, even mono- or bi-cytopenias should be evaluated for inherited bone marrow failure syndromes. Larger and multicenter studies would be useful to throw more light on the clinical spectrum of FA in children.

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