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# A Clinicopathological Study of Fanconi Anemia in a Tertiary Care Centre in Coastal India.

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**ABSTRACT**

Fanconi anaemia is a rare autosomal recessive disorder (birth incidence of 1 per 350000), characterized by chromosome instability that presents with a variety of congenital anomalies, progressive cytopenia, and susceptibility to the development of several malignancies. The study included cases that were diagnosed and treated at a tertiary care centre over a period of five years. The laboratory investigations including hemogram, peripheral smear, bone marrow aspirate and biopsy were correlated with the clinical, radiological and cytogenetic findings wherever available. A total of six cases of pancytopenia were confirmed to be Fanconi anaemia based on clinical, bone marrow and cytogenetic correlation (in two cases). Of the six cases studied, there were two pairs of siblings affected. The median age of diagnosis was six years of age. Of the six patients, three were males and three females. Bone marrow aspiration was done in all six cases and reported as hypoplastic marrow. Cytogenetic study was done in 2 of the cases which showed chromosomal breakage. Four out of the six had skeletal abnormalities. Three had organ abnormality with one having patent ductus arteriosis at birth, second case had multicystic dysplasia of bilateral kidneys and the third case had bilateral pelvic kidney. In the study, the patients presented with clinical features and haematological abnormalities suggestive of Fanconi anaemia with cytogenetic confirmation in 2 cases. Bone marrow failure resulted in death for four out of six patients.

**Keywords:** fanconi anemia, coastal, chromosome, hemogram.

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## INTRODUCTION

Fanconi's anemia (FA) is a genetically and phenotypically heterogeneous disorder, named after the Swiss paediatrician Guido Fanconi. It is characterised by variety of classical congenital abnormalities, progressive bone marrow failure that usually develops between the ages of 6 and 10 years, and predisposition especially to hematologic malignancies. Numerous congenital abnormalities have been reported in approximately 75% of patients with FA, and the most common of these abnormalities are skeletal (71%) (radial, hip, vertebral bones, rib), skin dyspigmentation (55%), short stature (51%), abnormalities of the eyes (23%) (microphthalmi and strabismus), renal and urinary tract abnormalities (34%), undescended testes and hypogonadism in males (20%), microcephaly (26%), low birth weight (11%), developmental disabilities (11%), hearing loss (9%), and structural renal and cardiac abnormalities (13%). Diagnosis of FA should be verified by identification of chromosomal instability by using DNA cross-linking agents such as diepoxybutane (DEB) or Mitomycin (MMC) in cell cultures.[1]

## MATERIALS AND METHODS

The study included six cases of pancytopenia that were diagnosed and treated at a tertiary care centre over a period of five years. The laboratory investigations included Peripheral Smear, Hemogram, Bone marrow aspirate and biopsy and DEB test. The cases were identified based on these criteria: a) Clinical presentation with congenital anomalies, b) Pancytopenia with hypocellular marrow, c) Radiological & cytogenetic analysis. An analysis of six cases of pancytopenia was done out of the 45 bone marrow cases that were found to have hypocellular marrow.

## RESULTS

CASE 1: A three year old male child presented to the pediatric out patient department with history of gum bleeding, ecchymotic patches and petechiae all over the body of 4 months duration. Developmental history was appropriate for age. There was no significant family history. On examination, the child was severely pale with ecchymotic patches all over the body. Systemic examination was normal. Laboratory investigations revealed a haemoglobin (Hb) of 4.3g/dl, total leukocyte count (TLC) 4800cell/cumm, platelet count 10,000cells/cumm, red blood cell (RBC) count 1.47 million /mm, packed cell volume (PCV) 13.7, mean corpuscular volume (MCV) 92.7 fl, mean corpuscular haemoglobin (MCH) 31.9pg, mean corpuscular haemoglobin concentration (MCHC) 34.4 g/dl, and erythrocyte sedimentation rate (ESR) of 85. Peripheral smear showed normocytic normochromic to macrocytic RBC with anisopoikilocytosis, low normal leukocyte count, a differential count (DC) showing neutropenia and platelets markedly decreased. A report of pancytopenia for evaluation was signed out. Patient was extensively evaluated outside with cytogenetic study done by peripheral lymphocyte culture confirmed Fanconi's Anemia. Bone marrow aspirate showed hypocellular marrow with increased lymphocyte and iron stores. Patient is on Stanazalol treatment and repeated blood transfusions.

CASE 2: A seven year old boy presented with failure to thrive and recurrent upper respiratory tract infection of six months duration. Perioral black discolouration was seen. A history of low birth weight of 1.25kg was provided by the parents. Developmental history was normal for age. The child had a younger sister with similar complaints. On examination, the child had severe pallor, prominent bat ears, perioral and tongue hyperpigmentation, hyperflexibility of first metacarpo-phalangeal joints and wrists. Upper segment: lower segment ratio was 1.05 and Arm span was 98cm. His weight was 8.1 kg and height 94cm which was suggestive of Grade 4 protein energy malnutrition (PEM) and grade 4 stunting. Systemic examination revealed a S1S2 grade 2/5 systolic murmur in the mitral area. Laboratory investigation showed Hb 1.9g/dl, TC 4870 cells/cumm, platelet count 18,000cells/cumm, differential count showed neutropenia, and ESR was 120. The reticulocyte count was 0.7%, MCV 120 fl, MCH 39.6 pg and MCHC 32.8g/dl. Peripheral smear revealed normocytic normochromic anemia with anisopoikilocytosis, macrocytosis and severe thrombocytopenia. Bone marrow aspirate showed features of hypoplastic marrow. Bone marrow biopsy confirmed aplastic anemia. The child passed away due to bone marrow failure and infection.

CASE 3: A five year old girl presented with poor weight gain and weakness and recurrent respiratory tract infections. She had an elder sibling (Case 2) who passed away a year ago. On examination, the child was pale with multiple white macular lesions all over the body. Grossly the head was small with head circumference less

than two standard deviation. The child had large bat like ears, bilateral aplastic thumbs and hyperflexible bilateral first metacarpophalangeal joints. Her height and weight were below the third percentile. Laboratory investigations revealed Hb of 4.4g/dl, total count 3930 cells/cumm, platelet count 14,000cells/cumm. Peripheral smear showed pancytopenia with sparsely distributed normocytic normochromic to macrocytic erythrocytes, neutropenia and thrombocytopenia. A year later she died secondary to bone marrow failure.

CASE 4: A 9 year old male presented with repeated lower respiratory infection with febrile convulsions at 1 year of age. His parents had a second degree consanguineous marriage. The patient's sister had same disease and expired of the same. On examination, his height, weight and head circumference were below the third percentile with microcephaly, microophthalmia, short stature, bilateral thumb aplasia (Figure 1A, 1B, 1C). Ultrasonogram of the abdomen showed multicystic dysplastic kidney and echocardiography revealed dilated cardiomyopathy. Investigations demonstrated Hb 6 g/dl, TC 5160 cells/cumm, platelet count 10,000cells/cumm. Peripheral smear showed microcytic hypochromic anemia with lymphocytosis with thrombocytopenia. Bone marrow aspiration showed hypocellular bone marrow. Patient is on repeated blood transfusions.

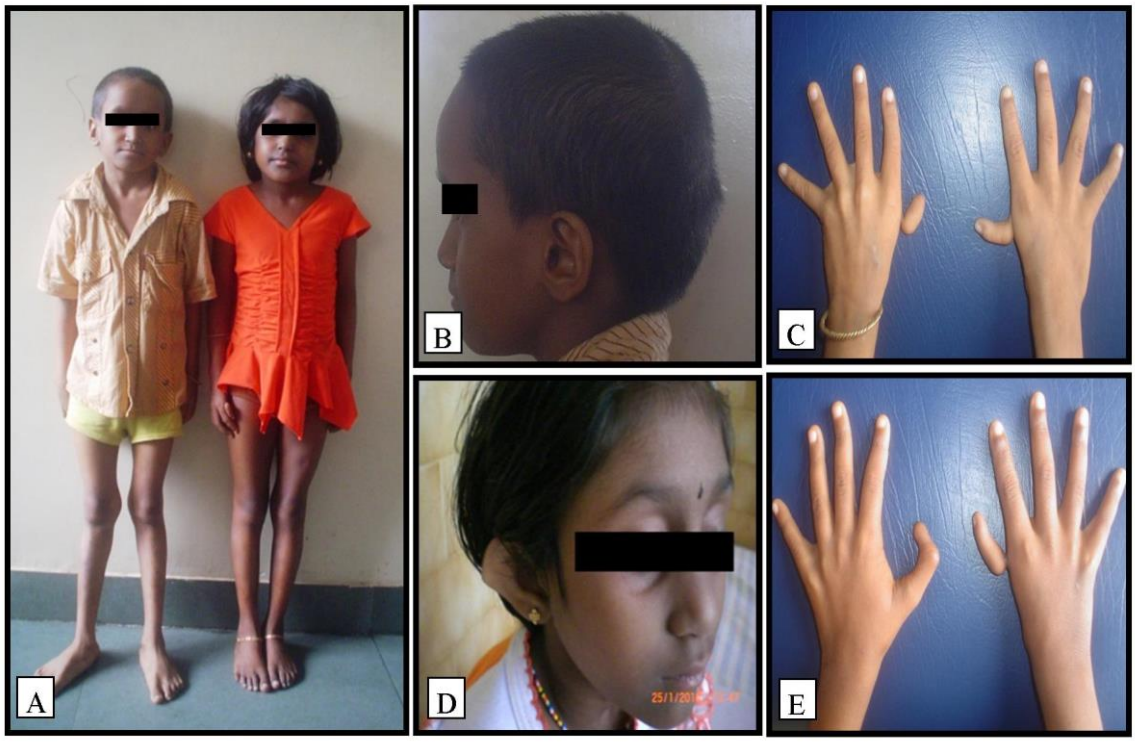


**Figure 1A: Siblings, 9 year old boy and his 10 year old sister with short stature; 1B: Microcephaly in the 9 year old boy; 1C: Bilateral thumb aplasia in the boy; 1D: Bat ears in the girl; 1E: Bilateral hypoplastic thumbs in the girl.**

CASE 5: A ten year old girl presented with microcephaly, bat ears, short stature and thumb hypoplasia (Figure 1A, 1D, 1E). Ultrasound abdomen showed bilateral pelvic kidney. Echocardiograpy revealed mild patent ductus arteriosus (PDA). Investigations showed Hb-10.3 g/dl, TC-2280 cells/cumm, platelet count 14000 cells/ cumm, MCV 91.3fl, MCH-30.3pg, MCHC 33.2gm/dl. Peripheral smear showed pancytopenia. Bone marrow aspiration and biopsy showed aplastic anemia. The girl passed away secondary to bone marrow failure.

CASE 6: A 14 yr old girl presented with recurrent lower respiratory tract infection and fever. She was diagnosed to have congenital acyanotic heart disease with left to right shunt with PDA at birth. PDA was closed at 7 months by coil closure. On examination head was small, microcephalic, marked pallor was seen, depressed nasal bridge and low weight and height for age. Laboratory investigations revealed Hb 6.8 g/dl, TC 2,200cells/cumm, platelet count 1o000 cells/ cumm. Peripheral smear showed Pancytopenia. Karyotyping was done. Chromosome analysis by G-banding showed 46 XX and multiple chromosomal abnormalities of breaks,

gaps and quadriradial configurations. Patient was on repeated blood transfusion. Her condition deteriorated over time and she finally succumbed to bone marrow failure and infections.

## DISCUSSION

The incidence of Fanconi's anemia is estimated to be approximately 3 per million with a carrier frequency of 1 in 300.[1] Males are affected slightly more frequently than females with a M:F ratio of 1.2:1.Although most of patients are diagnosed between 3 to 7 years of age based on the presence of pancytopenia, in 10%, the diagnosis is made after the age of 16,and the most frequent initial hematological manifestation is thrombocytopenia.[1,2] In our study, there was no sex predilection with median age of presentation being 6 years of age. The clinical manifestations included hyperpigmentation, café au lait spots, short stature, underweight, hypoplastic thumbs, microcephaly, pelvic kidneys, PDA, congenital acyanotic heart disease and dilated cardiomyopathy.

Progressive bone marrow failure with bone marrow examination results in reduced cellularity; it may be normocellular or hypercellular particularly in individuals evolving into myelodysplastic syndromes (MDS) or acute myeloid leukemia.[3] 50% of individuals who are initially found to have thrombocytopenia progress to pancytopenia within 3-4 years. The risk of MDS developing in FA patients is estimated to be approximately 6 %.

The most widely used diagnostic test for FA is hypersensitivity to the clastogenic (chromosome-breaking) effect of diepoxybutane (DEB) or Mitomycin (MMC).[3] In our study out of the six cases DEB chromosome breakage analysis was done only in 2 cases for confirmation. Unal et al presented a study of 5 cases of unrelated FA patients with growth retardation, café au lait spots, microophthalmia along with unusual organ pathologies like chronic obstructive lung disease, lipodystrophy, Sprengel's deformity, diaphragmatic hernia & inflammatory linear verrucous epidermal nevus respectively.[4]

Esmer et al found 12/34 (30%) FA patients among cases suspected of having FA on the basis of anemia, characteristic facial appearence, short stature, hyperpigmentation, renal or radial ray anomalies.[5] They performed the chromosomal breakage test in 34 patients with probable FA and 83 patients with clinical conditions that could suggest FA, 20 patients with aplastic anemia, 20 patients with VACTERL association, 20 with radial ray abnormalities, 7 with tracheo-esophageal fistulae, 12 with anal atresia, and four with myelodysplastic syndrome. They found 18 DEB positive patients: 12 were in the group of probable FA and 6 in the other groups.

Chromosomal breakage evaluation done by Korgaonkar et al showed 33 (17%) patients with classical FA, 9 (4%) with somatic mosaicism FA, (when at least 50% of the metaphases showed chromosomal breakage and radial figures), 25 (13%) with FA with high frequency of chromosomal breakage and without clinical features, and 128 (66%) with suspected FA but had no chromosomal breakage and clinical features of FA.[6,7]

In our study, out of the 6 cases, the remaining 4 cases were diagnosed to be Fanconi Anemia based on the clinical history, characteristic phenotypic features, peripheral smear and bone marrow findings & radiological correlation.

The risk of leukaemia developing is estimated to be between 5% and 10%.[8,9] In our study, all six cases showed pancytopenia with hypocellular marrow. Our patients had short survival, none of the four who expired had time for development of MDS or any other malignancies. The FA patients who survive to adulthood are around 50 times more likely to develop solid tumours compared with the general population and 29% develop a solid tumour by the age of 48 years.[10] In particular, there is a high risk of hepatic tumours (which may be related to androgen use) but also of squamous cell carcinomas of the oesophagus, oropharynx and vulva [8.9] A careful and specialized evaluation should be performed in patients where a suspicion of FA remains after initial testing, due to positive history, physical exam findings, and/or inconclusive chromosome tests in blood.[11,12]

## CONCLUSION

Fanconi anemia is one of several disorders that have in common the presence of increased chromosomal fragility or cellular hypersensitivity to mutagenic chemicals, associated with developmental

defects. Clinical diagnosis of FA is complicated because of other disorders, both genetic and non-genetic, are characterized by many of the clinical manifestations seen in FA. Information regarding DEB sensitivity is also extremely important in patients to be treated with bone marrow transplantation or chemotherapy.

**REFERENCES**


[1] Orkin S, David NG, Ginsburg D, Look TA, Fisher ED, Lux ES. In: Nathan & Oski's Hematology of Infancy and Childhood, 7th ed, Saunders Elsevier, PA. 312-29.

[2] Freedman MH. In: Nelson Textbook of Pediatrics. Stanton, St. Gessu, Schor, Behrman. 19th ed, Saunders Elsevier,PA. 1684-86.

[3] Auerbach AD. Mutat Res. 2009;668(1-2):4-10.

[4] Unal S, Ozbek N, Kara A, Alikas M, Gumruk F. Am J of Hemat 2004;77(1):50–4.

[5] Esmer C, Sanchez S, Ramos S, Molina B, Frias S, Carnevale A. American Journal of Medical Genetics 2004;124A(1):35–9.

[6] Korgaonkar S, Ghosh K, Jijina F, Vundinti BR. Journal of PediatricHematology/Oncology 2010;32(8):606-61.

[7] Korgaonkar S, Ghosh K, Vundinti BR. Hematology. 2010;15(1):58-62.

[8] Tischkowitz M, Dokal I. Br J of Haematology 2004;126(2):176–191

[9] Alter BP. Cancer 2003:97(2):425-40.

[10] Rosenberg PS, Greene MH, Alter BP. Blood 2003;101(3):822-6.

[11] Pinto FO, Leblanc T, Chamousset D, Le Roux G, Brethon B, Cassinat B, et al. Haematologica 2009;94(4):487-95.

[12] Huang T, Korson MS, Krauss C, Holmes LB. Am J Med Genet. 2002;111(2):178-81.