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Case Report

A rare manifestation of Fanconi anemia

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ABSTRACT

Fanconi anemia is an inherited pancytopenia, primarily inherited as autosomal recessive form. It occurs in all racial and ethnic groups. Majority of patients have both physical and haematological abnormalities, about one-third of patients will have normal physical features but abnormal haematological findings and unknown percentage have physical anomalies and normal haematological findings. The diagnosis is based on characteristic physical anomalies and abnormal haematological findings, which is confirmed with a lymphocytic chromosomal breakage study using Diepoxy butane (DEB). The report here is about a two and half years old female child who presented with physical features in the form of short stature, microcephaly, left hypoplastic thumb and congenital heart disease without haematological abnormalities. Chromosomal study was suggestive of Fanconi's anemia.

Keywords: Autosomal recessive, Fanconi anemia, Pancytopenia

INTRODUCTION

Fanconi anaemia is a rare genetically inherited autosomal recessive disorder characterised by congenital malformations, progressive pancytopenia, cellular hypersensitivity to DNA cross linking agent with predisposition to acute myeloid leukaemia (AML) and other malignancies.[1] The incidence of Fanconi anaemia is approximately 1to 5 per million.[2] The commonly associated genetic mutation in Fanconi anaemia are FANC genes. Sixteen distinct FANC genes have been reported among which, mutation in FANC-A are the most frequent.[3] These include microdeletions, large deletions, micro insertions and point mutations.[4] The disease is most commonly seen in children between 5-15 years.[5] Physical abnormalities are seen in 75% of affected individuals which includes short stature, hyperpigmentation of the skin and intertriginous areas, skeletal malformations of the upper and lower limbs, microcephaly along with multisystemic involvement like renal problems, hearing defects, cardiac disease, gastrointestinal problems, ophthalmic and genitourinary tract anomalies like hypogonadism (Table 1). Progressive bone marrow failure with pancytopenia typically present in first decade, often initially with thrombocytopenia or leucopoenia.[7] 20% of patients with Fanconi Anemia can develop cancers like AML, myelodysplastic syndrome, squamous cell carcinomas of the head and neck, oesophageal and tongue carcinoma, tumours of the liver, brain, skin, kidney, stomach and large bowel.[8]

Fanconi anaemia can be accurately diagnosed using DEB induced chromosome breakage which is highly specific. The cells of patients with FA are characterised by chromosomal hypersensitivity to cross linking agents and the resulting increase in chromosome breakage provides the basis for a diagnostic test.[9] The only proven long term cure of the bone marrow manifestations is successful allogenic hematopoietic stem cell transplantation (HSCT).[10]

Table 1: Various abnormalities present in Fanconi anaemia.[6]

Body	Abnormalities
Skeletal	Radial ray defects, hypoplasia of the thumbs and radial hypoplasia, congenital hip dislocation, scoliosis, and vertebral anomalies, microcephaly
Skin	Generalised skin hyperpigmentation, cafe au lait spots, and areas of hypopigmentation
Endocrinological	Growth hormone deficiency (with altered growth both in utero and postnatally) or hypothyroidism, or abnormalities of glucose/insulin levels
Eyes and ears	Microphthalmia, conductive deafness
Renal tract	Unilateral renal aplasia, renal hypoplasia, or double ureters
Genital tract	Hypogenitalia, hypospadias, and infertility (males), Underdeveloped genitalia and uterine anomalies (females)
Gastrointestinal tract	Atresia (oesophageal, duodenal, jejunal), imperforate anus, tracheo-oesophageal fistulae
Cardiac	Patent ductus arteriosus, ventricular septal defect, pulmonary stenosis, aortic stenosis and coarctation
Nervous system	Hydrocephalus, absent septum pellucidum, and neural tube defects

CASE REPORT

Two and half years old female child presented with failure to gain adequate weight since birth.

Figure 1: Facial dysmorphism-microcephaly, broad nasal base, micrognathia, epicanthal fold.

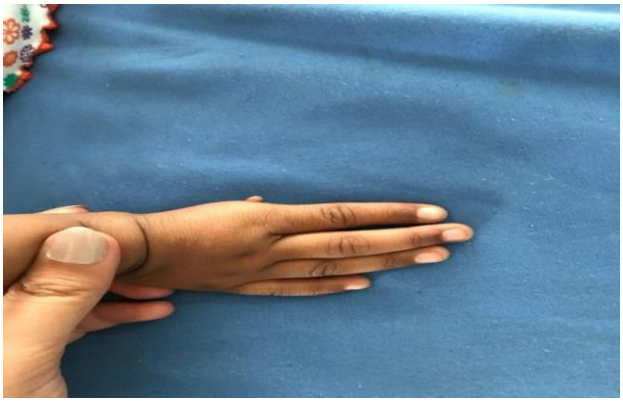

Figure 2: Right hypoplastic thumb.

Figure 3: Short stature.

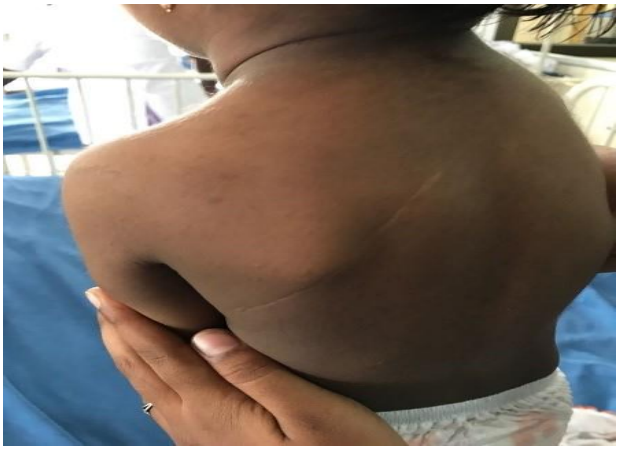

Figure 4: Surgical scar of PDA repair.

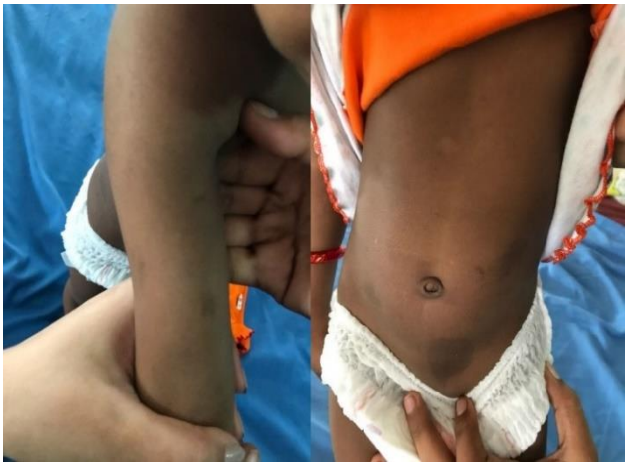

Figure 5: Multiple Café au lait spots.

This child was first born of non-consanguineous parents. On examination child had dysmorphism in the form of microcephaly, epicanthic fold, broad nasal base, micrognathia (Figure 1), hypoplasia of right thumb (Figure 2), short stature (Figure 3) surgical scar over the left side of the back-operated for the PDA (Figure 4) with multiple café-au-lait spots over trunk and arms (Figure 5).

Her anthropometry was suggestive of short stature height-76 cm (<-3SD) with microcephaly head circumference-41 cm (<-3SD). There was no pallor; vital signs were within normal limits. Systemic examinations were normal. Ophthalmic and hearing examination were normal. In view of thumb anomaly and congenital heart disease possibility of Holt Oram and TAR syndrome was considered. On investigation Complete blood count was normal, USG abdomen showed horse shoe kidney (Table 2). X-ray radius was normal. Genetic opinion was obtained, and cytogenetic report was suggestive of Fanconi anemia (Table 3).

This child was born elsewhere, preterm-33weeks via labour naturalis with birth weight of 1.9kg. Baby was admitted in NICU for 10 days for respiratory distress. Evaluation showed normal haemogram and chest X-ray. ECHO showed large PDA with left to right shunt. Child underwent surgical repair for the same at 1 year of age. Child did not have significant bleeding or pallor requiring blood transfusion.

Investigation

USG abdomen:

Table 2: USG abdomen findings.

	Observations
Liver	Normal in size and echo texture. No focal lesion seen. CBD is not dilated. Portal vein appears normal.
Gall bladder	Normal in contour and shows uniform wall thickness. There is no calculus seen.
Spleen	Normal in size and echo texture.
Pancreas	Normal head, body and tail. Main pancreatic duct is not dilated.
Kidneys	RT: Measure 3.8 x 2.0 cm, LT: Measure 3.7 x 1.8 cm. Bilateral kidneys are lower in position. There is fusion across the midline of two district fucntioning kidneys one on each side of the midline, connected by an isthmus of thickness 1.2 cm. Bilateral renal parenchyma appears normal.
Urinary bladder	Empty.

Interpretation: fusion of lower poles of both kidneys by an isthmus in the midline suggestive of horseshoe kidney. Chromosomal analysis by mitomycin C (MMC):

Table 3: Chromosomal breakage study.

	Patient	Control
Mean chromosome breakage/ metaphase (+MMC)	3.9	0.06
Mean radial formation/ metaphase (+MMC)	0.28	0
Mean chromosome breakage/ metaphase (-MMC)	0.14	0
Mean radial formation/ metaphase (-MMC)	0	0

Specimen: peripheral blood

Indications: multiple congenital anomalies, Fanconi anaemia.

Interpretation: cytogenic evaluation from 50 metaphases from phytohemagglutinin stimulated (72 hours) and Mitomycin C induced (48 hours) peripheral lymphocyte cultures revealed high frequency of chromosomal breakage as compared to control.

DISCUSSION

Fanconi anemia (FA) is the most common inherited bone marrow failure syndromes. Approximately 75% of them are between 5-15 years of age at time of diagnosis. In present case child is two and half years of age at diagnosis. Majority of patient will have both physical anomalies and abnormal haematological findings. Unknown percentage will have physical anomalies without haematological findings. Present child belongs to this rare manifestation of only physical anomalies without any haematological findings. Child did not have

significant bleeding or pallor requiring any blood transfusion in the past.

Fanconi anaemia closely mimics Holt Oram and TAR syndrome, as all of them are associated with congenital heart disease and limb anomalies. In present child x-ray both hands did not show any radial abnormalities and complete blood count showed no thrombocytopenia hence TAR Syndrome was ruled out. Holt Oram syndrome also called atrio-digital syndrome is an autosomal dominant disorder. This syndrome may include thumb abnormality like triphalangeal thumb, thumb hypoplasia, an absent radial bone in the forearm with atrial septal defect as prominent manifestation in the heart.[11] Though present case had thumb hypoplasia with PDA, other features-short stature, microcephaly, multiple cafe-au-lait spots were more consistent with Fanconi Anemia.

CONCLUSION

To conclude high index of suspicion is required to diagnose Fanconi Anemia as unknown percentage of them presents with physical anomalies without having haematological findings This child is on regular follow up to monitor for progression of bone marrow failure. Genetic counselling has been given to the parents as this is the first child. Successes with HSCT have dramatically improved the outlook. Careful surveillance for known complications, especially cancer and prompt intervention on their detection has also contributed to the improved survival.

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