Fanconi's Anaemia

*Joshi Rw,**Chalwade R,***Nakhale B.D, #Joshi P.P, *Bhagat J

Introduction

Fanconi anaemia is a rare auto somal recessive genetic disorder associated with congenital anomalies, aplastic anaemia and a predisposition towards haematological malignancies and solid tumors. These patients exhibit spontaneous as well as DNA cross link agents induced chromosomal breakages and gaps.

This is an important diagnostic tool and also helps to distinguish fanconi anaemias from other inherited aplastic anaemias. Recently 13 genes have been identified with the fanconi phenotype[1] Korgaongar ghosh et al.

We report a 14 year old boy with fanconi anaemia. He presented with increased lassitude and exertional dyspnoea since 5 years age.

On further interrogation, he revealed that he was admitted twice to the hospital with similar complaints. On both occasions, he was given blood transfusions and oral iron on discharge. There was no history of consanguity among parents and he was a single child.

On examination, we found him to be short statured [Height< -2SD]. The child was severely pale [Hb – 2.2g%] but had no petechiae and no sternal tenderness. There were no palpable lymph nodes, spleen or liver. He had no other skeletal abnormalities. External genitalia was normal. Ultrasonogram of abdomen revealed no abnormality. Echo cardiography was normal.

On haematological examination, we found that he had a pancytopenic picture. His bone–marrow was immediately done and was hypo cellular. No abnormal cells were detected [<10% cellularity] With this picture of pancytopenia and hypo cellular marrow in a young boy we thought of a differential diagnosis of F.A., Dyskeratosis Congenita, Shwachman Diamond syndrome and Diamond Blackfan anaemia. Accordingly his peripheral blood was sent for chromosomal breakage studies. This demonstrated breakages and gaps, which were suggestive of Fanconi anaemia. Response to androgens and growth factors were not very encouraging. Anaemia was however abetted with whole blood transfusions. Patient was advised bone marrow transplant.

Discussion

In 1927, Fanconi described a family in which 3 male children between 5 to 7 years of age presented with birth defects and pancytopenia. Based on his observations of this family and others, Fanconi's chief criteria for diagnosis included, pancytopenia, hyper pigmentation, small stature, skeletal malformations and familial occurrence. This was the basis for diagnosis of FA for many decades until the advent of chromosomal breakage studies. Between 1927 and 2001 only 1300 cases of FA were reported worldwide.

FA occurs in all races and ethnic groups. It is reported to have a carrier frequency of 1 in 300. Upto 0.5% of general population may be heterozygous at a FA locus. However, cells from carriers do not have sensitivity to DNA cross linking agents. Inherited Pancytopenia with a hypocellular marrow encompasses a few conditions viz. FA, Dyskeratosis Congenita, Shwachman Diamond syndrome and Diamond Blackfan syndrome. Dyskeratosis congenita presents with leukaplasia, dystrophic nails, reticular hyper pigmentation and aplastic anaemia. In Shwachman Diamond syndrome AA is associated with pancreatic insufficiency and malabsorption. Diamond Blackfan syndrome also presents with AA and congenital anomalies. Chromosomal breakage is an important diagnostic test, which differentiates FA from the above inherited bone marrow failure syndrome. Most commonly FA is associated with mutation in FANCA.

The phenotype of FA may present with short stature, radial ray deformities, microphthalmia, microcephaly, café – au – lait spots, cardiac and urogenital anomalies

along with the predominant picture of aplastic anaemia. The REFAIN study found consanguity in 64% while Korgaonkar, Ghosh et al reported it in 36.4% for parents of patients with FA.

The International Fanconi Anaemia Registry (IFAR) has shown that the spectrum of various associations with FA has further widened and now encompasses various endocrinal abnormalities Subjects with FA are shown to be growth hormone deficient. Abnormal glucose metabolism obesity dyslipidaemia and osteopenia and at times even metabolic syndrome is seen in FA. This syndrome is strongly associated with hematological malignancies like acute myeloid leukemia and other solid tumors. By the age of 30 years about 40% would have developed malignant transformation.

Apart from spontaneous or induced chromosomal breakage using either DEB (Diepoxybutane) or MMC (Mitomycin C); FA can also be diagnosed by using cell cycle analysis by cytometric methods on lymphocytes or fibro blasts.

Subjects with FA respond poorly to immuno suppression and growth factors. However, bone marrow transplant and stem cell transplant show encouraging results.

We conclude that in a young individual with inherited bone marrow failure a diagnosis of fanconi' anaemia should be entertained even in the absence of a typical phenotype.

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