Growth Hormone Deficiency in Fanconis Anemia

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Abstract Two cases of Fanconis anemia (FA) are reported here. Case 1 presented with hypoplastic anemia and skeletal abnormality. Case 2, his older brother had stunted growth, investigations detected growth hormone deficiency and mild hematological derangement without other endocrine abnormality. FA was confirmed by positive chromosomal breakages studies in both cases.

Keywords Fanconis anemia · Growth hormone deficiency · DNA breakages study

Most reports on Fanconis anemia (FA) are concerned with hematological problems. However, some physical characteristics suggest additional endocrine defects. We report two cases of FA in a family, Case 1, a 4 year old boy presented with hypoplastic anemia and skeletal abnormality without endocrinological problem. Case 2, older brother presented with short stature, investigations detected mild hematological derangement with growth hormone (GH) deficiency without other endocrine abnormality. In both

cases FA was confirmed by positive chromosomal breakages studies.

Case Report

A 4 years old boy presented with weakness and pallor for 4 weeks and bilateral abnormal thumb since birth. Family history revealed that his parents and older sister were absolutely normal. His older brother was other wise well but had significantly short stature.

Examination detected; moderate pallor without bleeding spots, lymphadenopathy, organomegaly or bone tenderness. Skeletal survey revealed total absence of right thumb and hypoplasia of left thumb (Fig. 1). Systemic examinations were unremarkable.

Investigations revealed: Hb 6.50 g/m³, total leukocyte count was 3,800 (neutrophil 55%, lymphocyte 41%, monocyte 02%, eosinophil 02%) platelet count of 72,600/m³, ESR 60 mm/first hour. Red cell population and platelet was reduced on smear. Bone marrow examination detected hypocellular marrow, which was mostly composed of fat, lymphomononuclear and plasma cells. Cells of normal hematopiosis was seen but markedly reduced. Mild dyserythropiosis were also noted involving myeloid, megakaryocytic and erythroid lineage of cell. Blast cells are not increased. X-ray wrist (right) showed hypoplastic first metacarpal and single phalanx with soft tissue fusion in between thumb and index finger (Fig. 2). X-ray wrist (left) showed only three carpal bones; metacarpal and phalanges are normal. Echocardiography, Ultrasonography of abdomen and scrotum, magnetic resonance image (MRI) of brain did not detect any abnormality. Thyroid glands scan and function test; glucose tolerance test (GTT) and GH assay with insulin stimulation was within normal limit.

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Fig. 1 Bilateral thumbs abnormality

Fig. 3 X-ray wrist showing bone age of 3–4 years

Fig. 2 X-ray wrist (right) showing hypoplastic first metacarpal and single phalanx with soft tissue fusion in between thumb and index finger

Chromosomal analysis showed a normal 46 XY karyotype and Mitomycin C (MMC) chromosomal stress test observed increased in percentage of chromosomal breaks and radiation formation in the patients sample in comparison to control which was suggestive of FA.

Case 2

Clinical examination of his older sister detected no abnormality but his 7 years old brother had significant growth retardation. He was in class III with normal intellectual development. He was a product of non-consanguineous marriage and normally delivered after an uncomplicated full term pregnancy with birth weight of 2.6 kg. Record of length was not available.

Examination revealed; proportionate short stature without facial dysmorphism, obvious skeletal abnormality, cryptorchidism or skin pigmentation. His height was 100.5 cm (<third centile) and weight was 16 kg (<third

centile); volume of the testis and pubic hairs were pre pubertal in nature. His mid parental height (MPH) was 170 cm. Except mild pallor clinical examinations were non-contributory.

Investigation revealed; Hb 8.5 g/dl, TLC was $4500/\text{m}^3$ (neutrophil 70%, lymphocyte 26%, eosinophil 04%), platelet count was $1,70000/\text{m}^3$. Peripheral smear showed RBC populations were predominately normocytic and hypochromic, a few macrocytes were also seen with normal platelet count. Bone marrow biopsy revealed hypocellularity with loss of myeloid and erythroid precursors and normal megakaryocytes population and features of mild dyserythropiosis. X-ray of (left) wrist showed bone age between 3 and 4 years (according to Greulich–Pyle method) (Fig. 3). Echocardiography and MRI brain was within normal limit. USG of abdomen detected bilaterally normally situated adrenal glands, kidneys and testis. The thyroid gland scan yielded a normally located gland. Thyroid function test and GTT was within normal range. Insulin hypoglycemic test was used as GH provocation in two different occasions, which the peak of GH level was 5 and 6 ng/ml (normal peak is >10 ng/ml). IGF-1, IGF BP3 was not done. Chromosomal analysis showed a normal 46 XY karyotype and MMC chromosomal stress test was suggestive of FA (Fig. 4).

Due to economic constrained bone marrow transplantation was not possible; GH replacement was not done because it may causes leukemic transformation. The younger brother was treated with packed cell transfusion and subcutaneous G-CSF along with intramuscular nandrolone decanoate (Deca-Durabolin 2 mg/kg/week) and oral prednisolone (40 mg/m²/alternate day). The older brother's hematological abnormality was mild and steroid may further reduce the growth potentially. So, he was put on follow up without active intervention.

Even after 6 months of therapy the younger brother showed no improvement. He had progressive pallor with

Fig. 4 Chromosomal study showing XY karyotype with increased breakage

thrombocytopenia and later became transfusion dependent. After 12 months, the older brother also showed progressive pallor and purpura. At that time he was also put on intramuscular nandrolone decanoate along with alternate day prednisolone, which had shown transient improvement but after that they were loss to follow up.

Discussion

FA is an autosomal recessive disorder characterized by bone marrow hypoplasia, congenital anomalies involving skin, heart, genitourinary tract, skeletal system, central nervous system, growth and mental retardation. Most reports on FA are limited to hematological aspects. Nilsson pointed out that cryptorchidism; abnormal pigmentation and stunted growth may be related to endocrine dysfunction [1]. Pochedly et al. first time documented impaired secretion of GH [2]. Other reported endocrinological abnormalities are abnormal adrenocorticotrophic hormone (ACTH) function, primary hypothyroidism, gonadotropin deficiency and missing insulin release following arginine stimulation [2–4]. Multiple endocrine abnormalities such as hypoplasia of the pituitary, thyroid, adrenal gland, ovaries were also reported [5]. Our first case had pancytopenia with skeletal abnormality without endocrinal abnormality. In our second case, the older brother had stunted growth with documented GH deficiency without other skeletal abnormality, pigmentation or cryptorchidism. His GTT thyroid gland scan and function test were within normal limit. His testis and adrenal glands were anatomically normal but hormonal assay was not done.

Although previous case report had shown that partial or complete absence of the corpus callosum and/or septum

pellucidum, holoprosencephaly with pituitary stalk interruption syndrome (PSIS) and septo-optic dysplasia, thickened pituitary stalk was associated in patient of FA with short stature and documented GH deficiency [6]. Our patient had documented GH deficiency without any pituitary gland abnormality detected by brain MRI.

The incidence of short stature in FA is estimated more than 50% and several case reports have specifically implicated growth hormone deficiency (GHD) as the cause [2, 4]. Other than GHD, DNA repair abnormalities may also contribute to growth failure. Due to that reason, some patients do not respond to GH treatment as completely as one might expect [2]. Associated hypothyroidism and treatment with androgen are also responsible for reduced growth. Birth weight of our patients was normal but intrauterine growth retardation is documented in FA patient.

Diagnosis of FA requires high index of suspicion as like our second case it may not be associated with hematologic abnormalities at presentation. Early diagnosis in FA is very important as long term survival depends on the age of onset of hematologic abnormalities or malignancies. If FA is recognize in the pre-anemic phase, drugs and environmental insults implicated in acquired aplastic anemia or malignancy can be avoided and life span can be prolonged. FA cells have increased spontaneous chromosomal breakage that is amplified by the addition of the cross-linking agents, diepoxybutane (DEB) or MMC. Similar spontaneous, but not DEB induced, chromosomal changes are observed in Bloom's syndrome and ataxia telangiectasia. For FA the DEB test is highly sensitive and specific and it is used in prenatal diagnosis also [7].

As like our cases, most patients require supportive care for BM failure. FA patients respond transiently to therapy with androgens and the cytokines, granulocyte-macrophage colony-stimulating factor (GM-CSF) and G-CSF [8]. Only curative therapy till date is allogenic BM transplant with histocompatible sibling donor. Early diagnosis also offers options of planning next pregnancy; as the umbilical cord blood can be used for stem cell transplantation [9].

Conflict of interest None.

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