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CASE REPORT

Fanconi Anemia — Case Report of Rare Aplastic Anemia at Child

Deaconu Alina[1], Vodă Daniela[2], Bulucea D[3]

[1] Children Hospital of Braşov, Romania
[2] Department of Medical and Surgical Specialties, Faculty of Medicine, Transilvania University, Braşov, Romania
[3] Faculty of Medicine, University Medicine and Pharmacy, Craiova, Romania

Introduction: Fanconi anemia is an autosomal recessive disease characterized by congenital abnormalities, defective haematopoiesis, and a high risk of developing acute myeloid leukaemia, myelodysplastic syndrome and cancers. FA was first described in 1927 by the Swiss pediatrician Guido Fanconi. The diagnosis is based on morphological abnormalities, hematologic abnormalities (pancytopenia, macrocytic anemia and progressive bone marrow failure) and genetic tests (cariograma).
Case report: We present the case of a child with Fanconi anemia. Although skin and bone morphological abnormalities were present from birth, diagnosis was suspected at 11 years old.
Conclusions: Fanconi anemia is a heterogeneous condition that can present a variety of congenital defects but invariably results in defective haemopoiesis, which is the major cause of morbidity and mortality.

Keywords: Fanconi anemia, pancytopenia, thrombocytopenia, chromosomal instability, FANC genes

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Introduction

Fanconi anemia (FA) is an autosomal recessive disease first described in 1927 by the Swiss paediatrician Guido Fanconi. Fanconi described a familial form of aplastic anemia in three brothers with abnormalities (short stature, hypogenitalism and skin pigmentation) [1]. Since then, over 900 cases have been reported. The prevalence of FA is 1 to 5 cases per 1 million persons and the heterozygous carrier frequency is about 1 case per 300 persons [2]. The ratio between sexes is about equal. FA is diagnosed at children aged between 5 and 15 years, and is characterized by progressive bone marrow failure and increased predisposition for acute myeloid leukemia and solid tumors. At birth, the blood count is usually normal and macrocytosis is often the first detected abnormality, followed by thrombocytopenia and neutropenia. Patients with FA have immune deficiencies before bone marrow failure. Pancytopenia typically appears between the ages of 5 and 10, the median age of onset being 7 years old [3]. Clinically, the affected FA patient may present with bleeding, pallor and recurrent infections. Certain cytogenetic abnormalities are commonly seen in FA patients including monosomy 5 and monosomy 7 [4]. Chromosomal instability, especially on exposure to alkylating agents (mitomycin C or diepoxybutane) are useful for a diagnostic test [5]. Hypersensitivity to cross linking agents increase chromosome breakage and provides the basis for a diagnostic test. FA can be caused by mutations in at least 13 different genes. FANCA gene was first cloned in 1996 and it is one of the largest FA genes [6]. Over 100 different mutations have been reported. Six genes FANC have been cloned (FANCA, C, D2, E, F, G) [3,7–10]. It would also be interesting to determine whether inherited polymorphisms in Fanconi anemia genes, resulting in more subtle defects in the expression or function of FA proteins, can contribute to an increase in cancer risk [11]. Since patients with Fanconi anemia have a characteristic clinical and cellular phenotype, the FA proteins presumably cooperate in DNA-repair pathway [12–16]. Positive diagnosis is based on various congenital physical anomalies, hematologic abnormalities (pancytopenia, macrocytic anemia and progressive bone marrow failure) and genetic tests. Bone marrow transplantation is the only treatment that definitively restores hematopoiesis at patients. In 2000 the median age at death reached 30, probably because of better medical care, compared to 1980 when median age at death was 20 and even less [4,9,11].

Case report

We report the case of an 11 year-old girl hospitalized in the Children's Hospital of Braşov, for the following reasons: pallor, fatigue, anorexia, productive cough, chest petechia elements. The onset of the disease was insidious with two weeks of cough. The patient followed an antibiotic treatment (amoxicillinum), without improvement.

From physiological and pathological history we noted: natural birth, premature at seven months, birth weight 900 g, only one hospitalization for growth restriction at the age of one year.

Clinical examination indicated a body mass index of 14.72 (weight 23 kg, height 125 cm), short stature, se-

Correspondence to: Alina Deaconu
E-mail: am_deaconu@yahoo.com

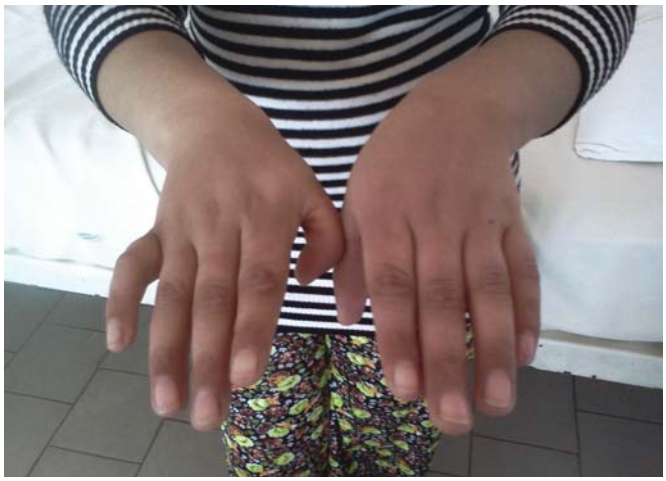

Fig. 1. Right thumb malformation

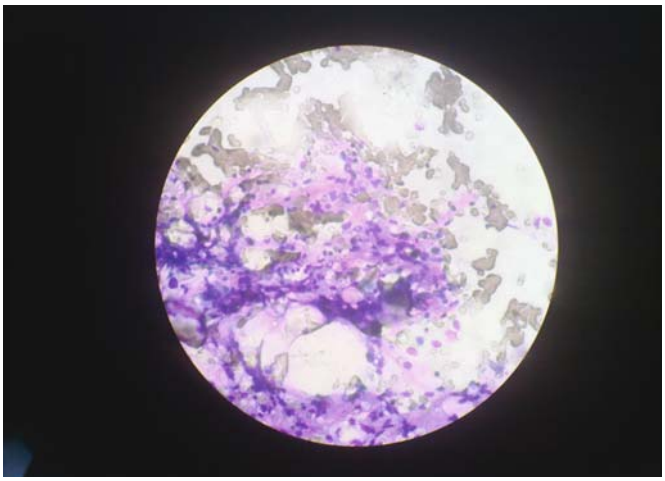

Fig. 2. Biopsy of bone marrow

vere general condition, afebrile, triangular looking face, hyperpigmentated skin, "café au lait" spots on the chest, right thumb malformation (Figure 1), bilateral bronchial rales, SaO_2 = 92%, rhythmic heart sounds, pulse = 80/min, blood pressure = 94/50 mmHg, systolic murmur of 2nd degree/6, slender abdomen, impalpable liver and spleen, diuresis present, no evidence of meningeal irritation signs.

Laboratory investigations revealed: pancytopenia (Leucocytes = 3700/mm^3, Hemoglobin = 10.3 g/dl, Thrombocytes = 31 000/mm^3), biological inflammatory syndrome (ESR = 70 mm/h, CRP = 2.37 mg), peripheral smear with moderate anisocytosis, relatively frequent macrocytes and macrothrombocytes, hemoglobin electrophoresis with high HbF levels, very high erythropoietin serum level.

Bone marrow puncture was performed to confirm the diagnosis, which revealed a bone with low cellularity, apparently without morphological modifications, confirmed by the biopsy which revealed a bone marrow with low cellularity (Figure 2).

By correlating clinical and laboratory data the presumptive diagnosis of Fanconi anemia is sustained by:

a) anamnesis (supernumerary thumb operated);
b) morphological abnormalities (short stature, triangular facies, looking pale, skin hyperpigmentation, café au lait spots on the chest, right thumb malformation, systolic murmur – ultrasound confirmed – intraventricular defect);
c) hematology (pancytopenia, bone marrow with low cellularity).

The treatment consisted in: antibiotherapy (Ceftriaxone 1 g × 2), intravenous immunoglobulin, corticosteroids (Prednison 1 mg/kg/day), gastric dressings, with favourable evolution: remission of fever and respiratory symptoms, slow growth in the number of leukocytes and platelets (Figures 3 and 4).

Discussions

FA is a very heterogeneous clinical condition and patients can present a large variety of abnormalities (Table I).

This condition should be distinguished from a variety of other diseases, such as:

– TAR syndrome (autosomal recessive syndrome characterized by radial aplasia and thrombocytopenia). Unlike FA, thumbs are invariably present bilaterally and there is no documented increase in haematological or solid tumor in TAR;
– Shwachman-Diamond syndrome (characterized by neutropenia and bone marrow aplasia, exocrine pancreatic insufficiency);
– Diamond-Blackfan anemia is characterized by de-

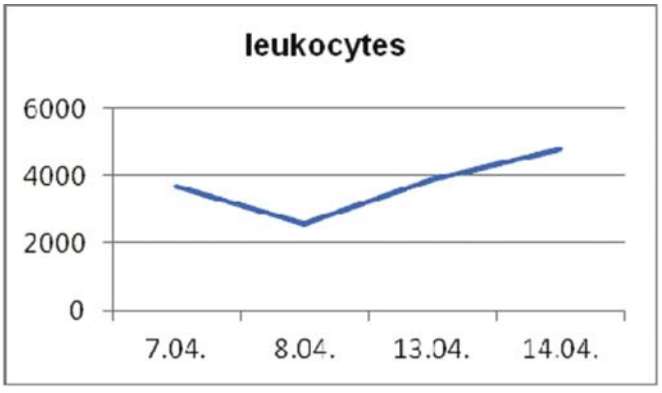

Fig. 3. Evolution of leukocytes

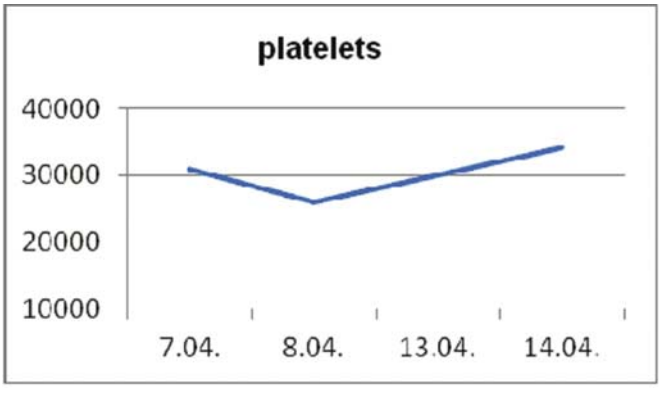

Fig. 4. Evolution of platelets

Table I. Variety of abnormalities present in FA

	Body	Abnormalities
1	Skeletal	Radial ray defects, hypoplasia of the thumbs and radial hypoplasia, congenital hip dislocation, scoliosis, and vertebral anomalies, microcephaly [18]
2	Skin	Generalised skin hyperpigmentation, café au lait spots, and areas of hypopigmentation [18]
3	Endocrinological	Growth hormone deficiency (with altered growth both in utero and postnatally) or hypothyroidism, or abnormalities of glucose / insulin levels [18]
4	Eyes and ears	Microphthalmia, conductive deafness [18]
5	Renal tract	Unilateral renal aplasia, renal hypoplasia, or double ureters [18]
6	Genital tract	Hypogenitalia, hypospadias, and infertility (males) [18] Underdeveloped genitalia and uterine anomalies (females)
7	Gastrointestinal tract	atresia (oesophageal, duodenal, jejunal), imperforate anus, tracheo-oesophageal fistulae [18]
8	Cardiac	patent ductus arteriosus, ventricular septal defect, pulmonary stenosis, aortic stenosis and coarctation [18]
9	Nervous system	hydrocephalus, absent septum pellucidum, and neural tube defects [18]

fective erythroid progenitor maturation and usually presents in the first year of life with normochromic or macrocytic anemia. Over one third have congenital malformations, often involving the head (micrognathia, cleft lip), upper limbs, and genitourinary system;

– Dyskerathosis (characterized by bone marrow aplasia, cutaneous hyper-pigmentation, short stature, but without visceral and skeletal abnormalities);
– Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disorder resulting from mutations in NBS1 gene, which codes for the nibrin protein (characterised by immune deficiency) [17].

Although skin and bone morphological abnormalities were present from birth in our patient, diagnosis was suspected only at the age of 11 years. Corticosteroids are not standard agreed treatment in FA. However, in our case corticosteroids (low doses) led to biological balance. We did not chose androgens, as our patient was female and we had to consider the side effects of androgens (masculinisation, acne, hyperactivity, growth spurt followed by premature closure of the epiphyses resulting in short stature, increase level of liver enzymes, risk of hepatic adenoma and adenocarcinomas). Androgens are used therapeutically because they enhance production and urinary excretion of erythropoietin and increase bone marrow cellularity [3,4]. Monitoring of liver function (liver enzymes, bilirubin, alpha-fetoprotein and liver ultrasound scans) is important during androgen therapy.

An endocrinological assessment should also be made in patients with FA (evidence of growth failure), and an ophthalmological assessment may show specific eye defects (microphthalmia, almond shaped palpebral fissures, and epicanthic folds). Plastic surgeons may consider correcting the defects in order to improve function and appearance [3,4].

Our patient had very high erythropoietin serum level. Other variables included the addition of potential growth factors, such as higher concentrations of erythropoietin, interleukin-3 (IL3), granulocyte-macrophage colony-stimulating factor (GM-CSF) which can improve hematopoiesis [3]. These cytokines led to small increases in burst-forming units – erythroid-derived colonies, but none completely compensated for the erythropoietic defect. In vitro bone marrow culture assays have shown defective hematopoiesis and altered levels of growth factors (such as reduced IL-6, GM-CSF, IL-1, and increased TNF-alpha) [18].

The only proven long-term cure of the bone marrow manifestations is successful allogeneic hematopoietic stem cell transplantation (HSCT) [9]. HSCT with donors other than HLA-identical is associated with high morbidity and poor survival. HSCT in FA is associated with a particularly high risk for transplantation-related events, including graft failure, and opportunistic infections [4].

Preimplantation genetic diagnosis was developed to help couples at high risk for transmitting genetic disease to accurately identify unaffected embryos before implantation [3,4].

Bone marrow failure typically develops during the first decade of life with an actuarial risk of 90% by 40 years of age [4]. A percentage of 20% of patients with Fanconi anemia develop cancers (acute myelogenous leukemia, myelodysplastic syndrome [19,20], squamous cell carcinomas of the head and neck, gynecologic squamous-cell carcinoma, esophag and tongue carcinoma, tumors of the liver, brain, skin, kidney, stomach, and large bowelgeal) [3,11,4]. A better understanding of the FA pathway may allow the development of strategies to correct the pathway, thus preventing carcinogenesis in patients with Fanconi anemia. Antioxidant therapy may be useful in delaying the onset of bone marrow failure or cancer [4].

Conclusions

Fanconi anaemia is a heterogeneous condition that can present with a variety of congenital defects. The main causes of morbidity and mortality are aplastic anemia, myelodysplasia, acute myeloid leukaemia, and solid tumours at older ages. For our patient the only proven long-term cure of the bone marrow manifestations is successful allogeneic hematopoietic stem cell transplantation.

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