

FANCONI ANEMIA – RARE CAUSE OF PANCYTOPENIA AT CHILD

**D. VODĂ¹ A. DEACONU²
A.S. MUŞAT²**

Abstract: *In this article we present two cases of children (sister and brother) who present Fanconi anemia. Fanconi aplastic anemia was discovered in 1927. In 99% of the cases it is transmitted autosomal recessive. The ratio between the sexes is about equal. It is usually diagnosed at children between 5-15 years. Positive diagnosis is based on the following criteria: 1. clinical (morphological abnormalities, anemic syndrome, infection, bleeding), 2. hematologic (pancytopenia, macrocytic anemia and marrow failure), 3. chromosome fragility.*

Key words: *Fanconi Anemia, pancytopenia, thrombocytopenia, FANC genes, bone-marrow failure.*

1. Introduction

Fanconi aplastic anemia was discovered by Fanconi in 1927 (see [5]), in 99% of the cases is autosomal recessive (patients are homozygous or double heterozygous for one or more mutations). X-linked transmission cases have been also described. It is usually diagnosed at children between 5 and 15 years, sex ratio is approximately equal to B / F = 1.3 / 1, approx. 10% are diagnosed in the neonatal period and 75% in the second decade of life. From the genetic point of view, have been described - FANC genes (see [9],[20]). The cells are hypersensitive to a number of oncogenic or mutagenic factors that determine chromosomal changes (rotations, angulation, fractures) [7], with inability of DNA to recover after the break[4],[6], the number of chromosomes remaining normal. Chromosomal fragility

test confirms the diagnosis. The first manifestation of disease is erythrocyte macrocytosis preceding thrombocytopenia and HbF is increased due to stress erythropoiesis.

2. Case report 1

Patient SE, female, 9 years old, with date of birth 19.05.1984, from rural areas, is hospitalized on 14.04.1993, by transfer from Făgăraş Hospital, for epistaxis, melena, chest pain, fatigue, fever.

Pathological history: Fanconi anemia, numerous admissions to Budimex Hospital (during the newborn period) and to Pediatric Clinic II Cluj-Napoca.

Clinical examination: feeling less than mediocre, febrile 39 celsius grade, Cushing face, anterior nosebleeds, pale skin with disseminated petechiae, bruising, craniofacial dysmorphism, multiple bone

¹ Faculty of Medicine, *Transilvania* University of Braşov.

² Children Hospital of Braşov.

malformations (no thumb metacarpals bilateral, absence of the first phalanx of the right thumb, right radius hypoplasia), lung bronchial rales, blood pressure = 85/50 mmHg, heart rhythm = 120 / min, SaO₂ = 94%, liver and spleen normal, mental retardation, without signs of meningeal irritation.

Laboratory investigations: pancytopenia with marked anisocytosis, numerous macro and megalocytes.

Investigations: Hb = 9.2 g / dl, Ht = 30.5%, Leucocytes = 1000 / mm³, platelets = 45000 / mm³, poor cellularity, represented by normal cell lines.

Abdominal ultrasound: horseshoe kidney, minimum degree of bilateral hydronephrosis.

Chest X ray evidenced right lobar pneumonia.

Evolution was with malaise, extreme pallor, disseminated petechiae, bruising at the puncture veins, conjunctival hemorrhage, tightened murmur, bronchial rales, productive cough, spontaneous and diffuse abdominal pain, "coffee grounds" vomiting, melena.

Treatment was complex and it consisted in: packed red blood cells, electrolyte rebalancing, anti-infective therapy, hemostatic therapy. The evolution was unfavorable, with hemorrhagic shock and infection: malaise, dizziness, extreme pallor, bruising to the tongue, "coffee grounds" vomiting, epistaxis, heart rhythm = 180 beats / minute, irreversible cardiopulmonary stop, resuscitation without success.

3. Case report 2

Patient S.I., male, age 11 years, rural areas, was hospitalized in the period 15.05-01.06.2007 in Brasov Children's Hospital, transferred from Fagaras Hospital by the following reasons: asthenia, fatigue, loss of appetite. Family history: sister died at 9

year old (Fanconi aplastic anemia), father died - brain tumor.

Pathological history: in the newborn period was operated for bilateral supernumerary thumb (polydactyly).

Clinical exam: G = 32 kg, T = 134 cm, short stature, dysmorph face (jet nose, small almond-shape eyes), pale skin - café au lait spots (fig. 2), thoracic kyphosis (fig. 1), short neck (fig. 1), postoperative scarring of bilateral thumb, double distal phalanx of the thumb, basal tightened vesicular murmur, cough, rhythmic heart sounds, systolic murmur of second degree, heart rhythm = 80 / min, diffuse painful abdomen on palpation, liver and spleen normal, diuresis present, external genital hypoplasia, no meningeal signs.

Laboratory investigations (16/05/2007): Leucocytes = 1800 / mm³, Neutrophils = 790 / mm³, RBC = 3,290,000 / mm³, Hb = 11.9 g / dl, Ht = 33.9%, MCV = 103fl, MCH = 36.2 pg, platelets = 56,000 / mm³, reticulocytes = 3‰, absolute number of reticulocyte: 987/mm³, inflammatory syndrome (ESR = 43 mm/1h), iron blood level = 109 µg / dl, ferritin = 131.70 ng / ml. Virological investigation was negative for acute infection: antibodies Cytomegalovirus IgG = 0.18 ISR (normal up to 0.09 ISR), IgM = 0.02 ISR (normal up to 0.07), antibodies Epstein Barr virus: IgG = 29.32 AU / ml (normal up to 20 AU / ml), IgM = 2.41 AU / ml.

Hemoglobin electrophoresis: HbA1 = 89.8%, HbA2 = 1.5%, HbF = 8.6%.

Peripheral smear: macrocytic red cells, anisocytosis, megalocytes and macrocytes, rare ovalocytes, schizocytes and dacriocytes, significant thrombocytopenia, average leukopenia, 6% lymphocytes with polymorphic aspect.



Fig. 1. Thoracic kyphosis



Fig. 2. Café au lait spot

Bone marrow aspiration: bone marrow fatty-looking, very poor cellularity, very rare marrow precursors, can not make quantitative assessments because of the poverty of the marrow. Bone marrow biopsy: bone trabeculae with modules replaced by fat, no hematopoietic elements, bone marrow aplasia. Chromosomal fragility test was positive.

Radiological examination: X-ray of neck: C5-C6 space reduced - this is partially block the spinal posterior vertebral arch pedicle C5, C6, without changes in bone structure.

Hand X-ray: double distal phalanx of the right thumb, dual distal phalanx of right ring finger, double proximal phalanx of left thumb.

Pulmonary lung X-ray: increased perihilar interstitial drawing.

Other examinations: Echocardiography - minimum aortic insufficiency. ENT and ophthalmological exam was normal.

Diagnosis: Aplastic Fanconi Anemia based on:

1. sister died with Fanconi anemia
2. clinical exam with dysmorph face, café au lait spots, cervical spine abnormalities, abnormalities of the hand bones, hypoplastic external genitalia
3. laboratory investigations with pancytopenia, poor of bone marrow cellularity
4. positive genetic test for chromosomal fragility.

Differential diagnosis of genetic causes of aplastic anemia:

1. Fanconi anemia (characterized by skeletal and visceral anomalies and pancytopenia)
2. Dyskeratosis (characterized by bone marrow aplasia, cutaneous hyperpigmentation, short stature, but without visceral and skeletal abnormalities)
3. TAR syndrome (characterized by radius aplasia and thrombocytopenia)
4. Shwachman-Diamond syndrome (characterized by exocrine pancreatic insufficiency, neutropenia and bone marrow aplasia)
5. Pearson syndrome (mitochondrial disease anemia and exocrine pancreatic insufficiency)
6. Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disorder characterised by immune deficiency, microcephaly, and hypersensitivity to ionizing radiation. [19].

Treatment: antibiotherapy, symptomatic treatment, corticosteroids: prednisone - 15 mg/day (from 25.05.2007), folic acid, C vitamin

Evolution with increase the number of leukocytes and platelets.

Recommendations: 1. Low sodium nutrition; 2. Treatment with Prednisone 15 mg/day; 3. Folic Acid, Calcium, vitamin C, D ; 4. Avoid cold and the infections, avoiding vaccines; 5. Weekly reevaluation with complete blood count.

Particularity of the cases: diagnosis delayed by lack of manifestation of pancytopenia, although morphological manifestations were present from birth.

Cortisone treatment improved clinical and hematological balance for the brother. The sister died with severe pneumonia with sepsis and severe bleeding secondary to severe pancytopenia.

In table 1 we present comparative the morphological abnormalities of sister and brother with Fanconi anemia with facial dysmorphism and thumb anomalies in both cases.

Comparative cases

Table 1

Anomalies	Case report 1 (SE, sister, 9 years old)	Case report 2 (SI, brother, 11 years old)
skin	without modification	café au lait spots on body, legs
facial	facial dysmorphism	facial dysmorphism (jet nose, small almond -shaped eyes)
bones	lack of bilateral thumb metacarpals, absence of first phalanx of right thumb, hypoplasia of the radius	thoracic kyphosis, short neck, double distal phalanx of the right thumb, dual distal phalanx of right ring finger, double proximal phalanx of left thumb.
heart	without modification	minimal aortic insufficiency
genital	without modification	hypoplasia of external genitalia
renal	horseshoe kidney, bilateral hydronephrosis of minimum degree	without modification

4. Discussions

Fanconi Anemia (AF) can be caused by mutations in different genes. Until recently, there were thought to be at least eight FA complementation groups determined by somatic cell hybridisation, FA-A, B, C, D1, D2, E, F, G (see [3], [9]). Six of the FA genes (FANCA, C, D2, E, F, G) have been cloned (see [20], [7], [11],[13],[14]). FANCA was cloned in 1996 and it is one of the largest FA genes (see [11], [17]). Over 100 different mutations have been reported.

In vitro bone marrow culture assays have shown defective hematopoiesis in FA and FA cells show altered levels of certain growth factors [2][3], such as reduced IL-6,

GM-CSF, IL-1b, and increased TNF-alpha [15].

Patients with FA have immune deficiencies before bone marrow failure. Pancytopenia typically presents between the ages of 5 and 10 years (see [7]). Sister died because of bleeding complications and sepsis with multiple organ failure and systems. The cases presented in this paper had skin, bone, heart, genitourinary abnormalities. The main causes of morbidity and mortality are aplastic anaemia, myelodysplasia [12], [18], acute myeloid leukaemia, and solid tumours at older ages [1].

If a diagnosis of FA is suspected, it should be confirmed by chromosome breakage studies using mytomicine B.

Many patients who develop bone marrow failure initially respond to supportive measures such as blood transfusions, androgens, and cytokines [17]. Androgens, usually oral oxymetholone, are often used therapeutically. Cytokines such as G-CSF and GM-CSF can improve haematopoiesis [17].

Most patients become refractory to therapy and the definitive treatment of choice is haematopoietic stem cell transplantation (see [11], [16]).

Recently, preimplantation genetic diagnosis for parents of a previously affected child has been used to select embryos (ethically controversial) (see [11]).

Many questions remain regarding the functions of FA proteins outside DNA repair and how these affect phenotype.

Correlation between the molecular defect and clinical manifestation is an important task to better diagnosis of subjects with FA [17].

References

- Alter, B.P.: *Fanconi's anemia and malignancies*. In: *Am J Hematol* **53** (1996), p. 99-110.
- Callen, E., Samper, E., Ramirez, M.J., Creus, A., Marcos, R., Ortega, J.J., Olive, T., Badell, I., Blasco, M.A., Surrallés, J.: *Breaks at telomeres and TRF2-independent end fusions in Fanconi anemia*. In: *Hum Mol Genet* **11** (2002), p. 439-444.
- Cheng, N.C., van De Vrugt H.J., van Der Valk M.A., Oostra A.B., Krimpenfort P., de Vries Y., Joenje H., Berns A., Arwert F.: *Mice with a targeted disruption of the Fanconi anemia homolog *Fanca**. In: *Hum Mol Genet* **9** (2000), p. 1805-1811.
- Escarceller, M., Buchwald, M., Singleton, B.K., Jeggo, P.A., Jackson, S.P., Moustacchi, E., Papadopoulo, D.: *Fanconi anemia C gene product plays a role in the fidelity of blunt DNA end-joining*. In: *J Mol Biol* (1998);279:375-85.
- Fanconi, G.: *Familiaere infantile perniziosaartige Anaemie*. In: *Jahrbuch Kinderheild* **117** (1927), p. 257-280.
- Futaki, M., Igarashi, T., Watanabe, S., Kajigaya, S., Tatsuguchi, A., Wang, J., Liu, J.M.: *The FANCG Fanconi anemia protein interacts with CYP2E1: possible role in protection against oxidative DNA damage*. In: *Carcinogenesis* (2002);23:67-72.
- Gush, K.A., Fu, K.L., Grompe, M., Walsh, C.E.: *Phenotypic correction of Fanconi anemia group C knockout mice*. In: *Blood* **95** (2000), p. 700-704.
- Joenje, H., Levitus, M., Waisfisz, Q., D'Andrea, A., Garcia-Higuera, I., Pearson, T., van Berkel, C.G., Rooimans, M.A., Morgan, N., Mathew, C.G., Arwert, F.: *Complementation analysis in Fanconi anemia: assignment of the reference FA-H patient to group A*. In: *Am J Hum Genet* **67** (2000), p. 759-762.
- Liu, J.M., Kim S., Read, E.J., Futaki, M., Dokal, I., Carter, C.S., Leitman, S.F., Pensiero, M., Young, N.S., Walsh, C.E.: *Engraftment of hematopoietic progenitor cells transduced with the Fanconi anemia group C gene (*FANCC*)*. In: *Hum Gene Ther* **10** (1999), p. 2337-2346.
- Koomen, M., Cheng, N.C., van De Vrugt, H.J., Godthelp, B.C., van Der Valk, M.A., Oostra, A.B., Zdzienicka, M.Z., Joenje, H., Arwert, F.: *Reduced fertility and hypersensitivity to mitomycin C characterize *Fancg/Xrcc9* null mice*. In: *Hum Mol Genet* 2002;11:273-81.
- MacMillan, M.L., Auerbach, A.D., Davies, S.M., Defor, T.E., Gillio, A., Giller, R., Harris, R., Cairo, M., Dusenbery, K., Hirsch, B., Ramsay, N.K., Weisdorf, D.J., Wagner, J.E.: *Haematopoietic cell transplantation in patients with Fanconi anaemia using*

- alternate donors: results of a total body irradiation dose escalation trial.* In: Br J Haematol **109** (2000), p. 121-129.
12. McCloy, M., Almeida, A., Daly, P., Vulliamy, T., Roberts, I.A., Dokal, I.: *Fludarabine-based stem cell transplantation protocol for Fanconi's anaemia in myelodysplastic transformation.* In: Br J Haematol (2001);112:427-9.
 13. McMahon, L.W., Sangerman, J., Goodman, S.R., Kumaresan, K., Lambert, M.W.: *Human alpha spectrin II and the FANCA, FANCC, and FANCG proteins bind to DNA containing psoralen interstrand cross-links.* In: Biochemistry (2001); 40:7025-34.
 14. Pang, Q., Fagerlie, S., Christianson, T.A., Keeble, W., Faulkner, G., Diaz, J., Rathbun, R.K., Bagby, G.C.: *The Fanconi anemia protein FANCC binds to and facilitates the activation of STAT1 by gamma interferon and hematopoietic growth factors.* In: Mol Cell Biol (2000);20:4724-35.
 15. Rosselli, F., Sanceau, J., Gluckman, E., Wietzerbin, J., Moustacchi, E.: *Abnormal lymphokine production: a novel feature of the genetic disease Fanconi anemia. II. In vitro and in vivo spontaneous overproduction of tumor necrosis factor alpha.* In: Blood **83** (1994), p. 1216-1225.
 16. Stark, R., Thierry, D., Richard, P., Gluckman, E.: *Long-term bone marrow culture in Fanconi's anaemia.* In: Br J Haematol **83** (1993), p. 554-559.
 17. Tischkowitz, M.D., Hodgson, S.V.: *Fanconi anaemia.* In: Journal of Medical Genetics **40** (2003), p. 1-10.
 18. van de Vrugt, H.J., Cheng, N.C., de Vries, Y., Rooimans, M.A., de Groot, J., Scheper, R.J., Zhi, Y., Hoatlin, M.E., Joenje, H., Arwert, F.: *Cloning and characterization of murine fanconi anemia group A gene: Fanca protein is expressed in lymphoid tissues, testis, and ovary.* In: Mamm Genome (2000);11:326-31.
 19. Varon, R., Vissinga, C., Platzer, M., Cerosaletti, K.M., Chrzanowska, K.H., Saar, K., Beckmann, G., Seemanova, E., Cooper, P.R., Nowak, N.J., Stumm, M., Weemaes, C.M., Gatti, R.A., Wilson, R.K., Digweed, M., Rosenthal, A., Sperling, K., Concannon, P., Reis, A.: *Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome.* In: Cell **93** (1998), p. 467-476.
 20. Waisfisz, Q., de Winter, J.P., Kruyt, F.A., de Groot, J., van der Weel, L., Dijkmans, L.M., Zhi, Y., Arwert, F., Scheper, R.J., Youssoufian, H., Hoatlin, M.E., Joenje, H.: *A physical complex of the Fanconi anemia proteins FANCG/XRCC9 and FANCA.* In: Proc Natl Acad Sci USA (1999);96:10320-5.