CASE REPORT

Fanconi Anemia: How to Recognize It Before Bone Marrow Failure?

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Abstract

Fanconi anemia is the most frequently inherited bone marrow failure syndrome. It is caused by genetic mutations that lead to genomic instability, which is the hallmark of the disorder. Therefore, patients are extremely vulnerable to bone marrow failure, leukemia, and neoplasms. Several physical anomalies have been associated with it, affecting multiple organ systems. We present three clinical cases in which the diagnosis was possible before the onset of marrow aplasia, highlighting the important clinical clues that physicians should be aware of.

Keywords: Bone Marrow Failure Disorders/etiology; Bone Marrow Failure Disorders/prevention & control; Child; Fanconi Anemia/complications; Fanconi Anemia/diagnosis; Infant, Newborn

Introduction

In 1927, pediatrician Guido Fanconi described three brothers who suffered from various birth defects and who died of a condition that resembled pernicious anemia.[1,2] Later, researchers were able to prove that they suffered in fact from chromosomal instability,[1] and the disease was named Fanconi anemia. Since then, more than 2,000 cases have been reported[2] and, to date, 23 genes have been identified.[3] Fanconi anemia is the most common of the inherited bone marrow failure syndromes.[3,4] Initially, children were diagnosed when they had an association of pancytopenia and physical congenital findings.[2] Thankfully, today, many are diagnosed before bone marrow failure. Therefore, clinicians should be aware of some physical and hematological clues in order to raise the suspicion of Fanconi anemia.

Fanconi anemia is an autosomal recessive disease, mostly due to FANCA gene mutation (65%), except Fanconi anemia complementation group B (FANCB), X-linked, and Fanconi anemia of complementation group R (FANCR), autosomal dominant.[3,5,6] These proteins are responsible for genomic stability, through the repair of deoxyribonucleic acid (DNA) interstrand crosslinks, but evidence also suggests that they are able to remove oxygen-free radicals, thereby decreasing oxidative stress.[4] Therefore, aberrant cell cycle regulation and premature cell death occur, which explains the multiple congenital defects, increased risk of bone marrow failure, and malignancies (mostly due to excessive susceptibility to toxic exposures).[4,5,7]

Phenotype is extremely heterogeneous, ranging from no physical abnormalities (25%) to multiple affected systems (Table 1).[8,9] The most common physical findings are abnormal skin pigmentation (40%-60%), short stature (40%-60%), and upper limb abnormalities (50%).[2,4-6] In addition, there is increasing evidence of a relation between Fanconi anemia and VACTERL-H association (vertebral abnormalities, anal atresia, cardiac defects, tracheoesophageal fistula, esophageal atresia, renal and radial abnormalities, limb abnormalities, and hydrocephalus).[5,6,8]

Most will have bone marrow failure (average onset at 7.6 years). Therefore, it is important to recognize the laboratory signs that often precede it, such as thrombocytopenia and red cell macrocytosis.[4,5,9] Progression to pancytopenia may occur rapidly, take months or years, or not develop at all (rarely).[5,7]

The diagnostic test for Fanconi anemia depends on the demonstration of chromosomal aberrations in blood T lymphocytes that are cultured with diepoxybutane or mitomycin C. However, some patients have hematopoietic somatic mosaicism and, therefore, it may be helpful to repeat the test on skin fibroblasts.[2,5,10] Gene sequencing is recommended to confirm the diagnosis and exclude other chromosomal breakage disorders.[5] It is also important to perform genetic studies in Fanconi anemia patient siblings and parents, recognizing affected individuals with milder phenotypes and potential hematopoietic stem-cell transplantation donors as well as to provide genetic counseling for

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the whole family.[3,5,11] Hematopoietic stem-cell transplantation is the only curative therapy for Fanconi anemia patients with aplastic anemia and hematological malignancies.[3,10] Currently, with early detection and adapted hematopoietic stem-cell transplantation, the median survival is greater than 30 years. Mortality and morbidity in adult life are mostly due to solid tumors, chronic graft-versus host disease, and iron-overload, justifying a long-term follow up.[9,11]

Case Report

Case 1

We report the clinical case of a 7-year-old girl, born at 38 weeks, small for gestational age, with a prenatal diagnosis of renal dysplasia. Her ultrasound exam showed a bicornuate uterus as well as ectopic and dysplastic kidneys. Regular laboratory tests with normal renal function but persistent macrocytosis (without anemia) and non-immune thrombocytopenia (minimum 80,000 cells/µL). On examination, she was thin (lower than third centile weight), short (Fig. 1), had six *café-au-lait* skin spots, birdlike facies, and low set thumbs (Fig. 2). Due to those physical features, kidney and uterus anomalies, thrombocytopenia, and macrocytosis, a bone marrow biopsy was performed, showing moderate hypocellularity. A diepoxybutane test was positive, and so a Fanconi anemia diagnosis was made. Genetic testing is currently underway.

Case 2

A female newborn, from consanguineous parents, had a brother with Fanconi anemia that died at age 7 from complications after hematopoietic stem-cell transplantation. Regarding this family history, a diepoxybutane test in amniotic fluid was made, ensuing a negative result. Unfortunately, no prenatal genetic test was performed at this time. After delivery, her physical exam revealed short height, broad nasal bridge, epicanthal folds, hypoplastic and low set right thumb, and altered skin pigmentation (Fig. 3). Considering the hypothesis of Fanconi anemia, a diepoxybutane test was repeated (in peripheral blood), thereby confirming the diagnosis. Genetic testing identified a homozygous mutation on exon 4 of the *FANCA* gene and heterozygosity in both parents. Ultrasound study documented horseshoe kidneys. Currently, she is 2 years old, has no cytopenias, and continues to attend regular follow-ups.

Case 3

A newborn with microcephaly, polydactyly (double thumb), and a *café-au-lait* skin spot was referred for a genetic consultation. No family history was present. The patient was tested for Fanconi anemia and had a *FANCA* gene mutation in homozygosity. Due to anemia (hemoglobin 8 g/dL), macrocytosis (mean corpuscular volume 94 fL) and thrombocytopenia (91,000 cells/µL), he was later referred to our hematological unit at 2 years old. The cardiac and abdominal ultrasound performed

Table 1. Main anomalies found in Fanconi anemia[2,4]

Anomaly	Frequency
Skin: hyper/hypopigmentation, *café-au-lait* spots	40%
Skeletal	
Short stature	40%
Microcephaly	20%
Face: triangular, birdlike, micrognathia	2%
Spine: hemivertebra, *spina bifida*, abnormal ribs	2%
Upper limbs	
Thumbs: absent or hypoplastic, low set, bifid	35%
Radii: absent or hypoplastic	7%
Hands: flat thenar eminence, clinodactyly, polydactyly	5%
Eyes: small, strabismus, epicanthal folds, hypo / hypertelorism	20%
Ears: deaf, dysplastic, abnormal shape	10%
Renal: horseshoe kidneys, ectopic or pelvic, hypoplastic, hydronephrosis	20%
Gonads	
Male: hypogenitalia, undescended testis, micropenis	25%
Female: hypogenitalia, bicornuate uterus	2%
Developmental delay	10%

were normal, while bone marrow aspirate and biopsy showed hypocellularity. Currently, he remains under regular surveillance and is clinically stable without bone marrow failure.

Discussion

These cases emphasize the clinical presentation of many children with Fanconi anemia: minor physical changes, several apparently unrelated malformations as well as persistent and unexplained thrombocytopenia/macrocytosis (frequently the first laboratorial sign). Clinicians should be aware of these clinical and laboratory signs in order to attempt an early diagnosis (as in our cases) that allows time for additional evaluation, preventing associated comorbidities and progression to bone marrow failure, while aiming for a preemptive hematopoietic stem-cell transplantation.

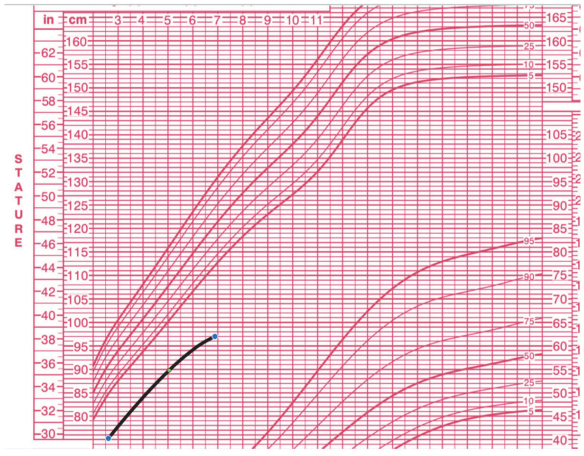

Figure 1. Height for age growth chart from patient 1, highlighting the girl's short stature.

In Fanconi anemia, hematopoietic stem-cell transplantation is the only curative treatment (for hematological disease) but requires an adjusted conditioning since conventional chemotherapy will cause further harm.[5,10,11] Androgen therapy also may be helpful, especially in those lacking a closely matched related donor, although only half will respond to it.[5,11] There are also some promising clinical trials with gene therapy that might be a strategy to overcome the associated bone marrow failure in the future.[3,9]

An important morbidity to consider in these patients is the chronic iron-overload due to frequent blood transfusions (because of pancytopenia), while a hematopoietic stem-cell transplantation is not possible. Genetic testing is crucial, particularly when a Fanconi anemia diagnosis exists in a family member, since there may be false results in the diepoxybutane test (as in case report 2). Therefore, each family member should be tested for Fanconi anemia in order to exclude other affected relatives and promptly find potential hematopoietic stem-cell transplantation donors.

Due to normal DNA repair loss, patients have an exceptionally increased risk of leukemia, myelodysplastic syndromes, and solid tumors, particularly head and neck squamous cells carcinoma. Up to one third of Fanconi anemia patients will develop a solid tumor, mostly in their second/third decades of life.[2,5,9,11] Unfortunately, hematopoietic stem-cell transplantation will not be helpful in this situation and, therefore, regular cancer surveillance and prevention is recommended. Each patient should be vaccinated for human papillomavirus, undergo annual laryngoscopy after age 10, and females must have a routine gynecological examination after menarche.[5,9,11] The multiple associated anomalies and persistent neoplastic risk in these patients demand a careful and multidisciplinary long-term follow-up.

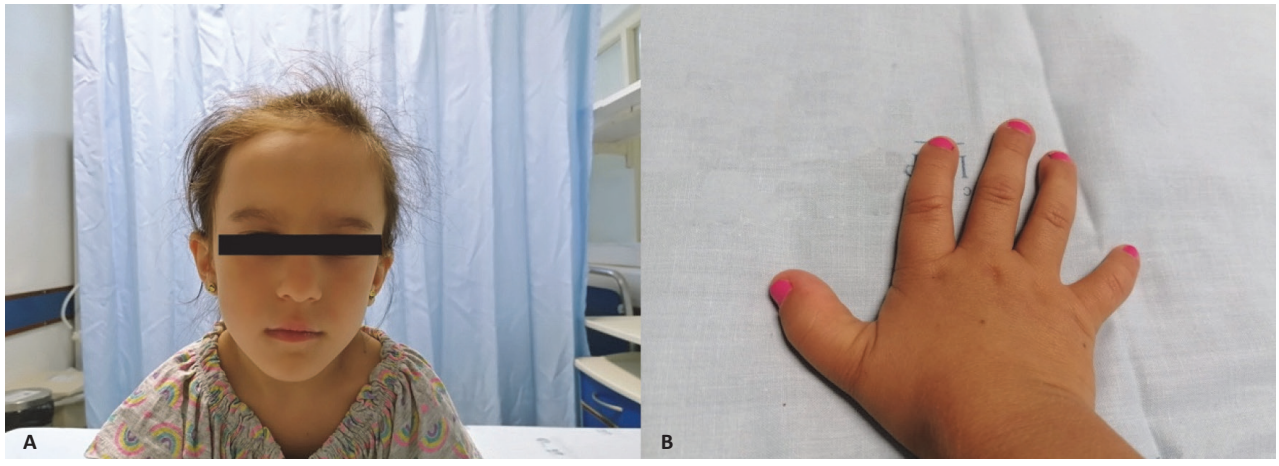

Figure 2. Patient 1 with birdlike facies (A) and low-set thumb (B).

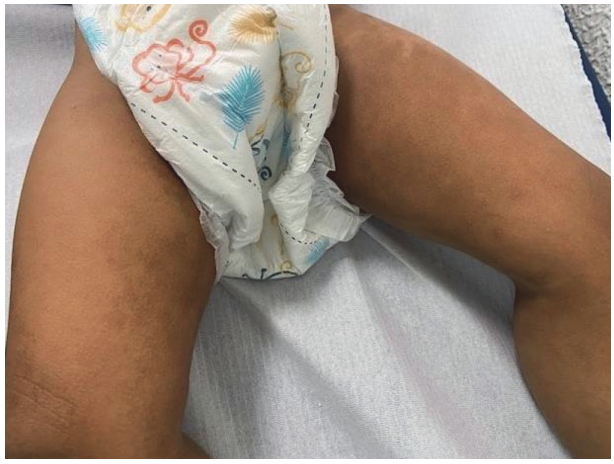

Figure 3. Patient 2 with hypo and hyperpigmented skin lesions.

WHAT THIS CASE REPORT ADDS

- Up to 25% of Fanconi anemia patients will not present any physical changes and most will have only minor and apparently unrelated physical changes.
- Pancytopenia is the disease's classic hallmark, but persistent thrombocytopenia and macrocytosis frequently precede bone marrow failure.
- Although the gold standard is a diepoxybutane or mitomycin C test (attesting chromosomal breakage), false negative results are possible and, therefore, genetic testing should be performed to confirm the diagnosis.
- Early diagnosis is extremely important to provide genetic screening to the family, particularly siblings, in order to find potential hematopoietic stem-cell transplantation donors, guarantee the appropriate treatment, and carry out long-term surveillance.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication

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Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Anemia de Fanconi: Como reconhecer antes de ocorrer Falência Medular?

Resumo

As síndromes de falência medular congénitas são entidades clínicas raras, sendo a anemia de Fanconi a mais frequente delas. É causada por mutações genéticas que causam instabilidade cromossómica, o que condiciona uma suscetibilidade aumentada para o desenvolvimento de aplasia medular, leucemia e outras neoplasias. São várias as alterações físicas associadas à síndrome e que podem atingir diversos sistemas de órgão. Apresentamos três casos clínicos nos quais foi possível chegar ao diagnóstico antes da falência medular, pretendendo-se dessa forma destacar os principais achados clínicos que devem alertar o médico para a doença.

Palavras-Chave: Anemia de Fanconi/complicações; Anemia de Faconi/diagnóstico; Criança; Recém-Nascido; Transtornos da Insuficiência da Medula Óssea/etiologia; Transtornos da Insuficiência da Medula Óssea/prevenção & controle