Clinical characteristics of patients with Fanconi anemia

Características clínicas de pacientes com anemia de Fanconi

Características clínicas de pacientes con anemia de fanconi diagnosticados en un servicio de genética clínica

Paulo Ricardo G. Zen[1], Felipe Nora de Moraes[2], Rafael Fabiano M. Rosa[3], Carla Graziadio[4], Giorgio Adriano Paskulin[5]

ABSTRACT

Objective: To investigate the clinical characteristics of Fanconi anemia (FA) patients diagnosed in a Clinical Genetics Service.

Methods: The study included all patients assisted in an university genetics service in Southern Brazil, between 1975 and 2008, with clinical suspicious of FA and submitted to the study of chromosomal breakage with diepoxybutane (DEB) from peripheral blood. A retrospective analysis of the clinical characteristics of the patients was carried out by a systematic survey of their medical records.

Results: 17 patients were studied and seven had a confirmed diagnosis of FA. Patients with FA were characterized by a broad phenotype, ranging from pancytopenia without dysmorphisms to multiple malformations and absence of hematological alterations. Certain findings, such as triangular face, prominent ears and café-au-lait spots were common and found only among individuals with FA. History of bruises, hematomas, petechiae, infections and lymphadenopathies was also common among individuals of this group. However, neurological alterations were observed only in patients without FA. Consanguinity was verified in one patient who presented FA.

Conclusions: Despite the limitations of this study, the findings show the great phenotypical variability observed in patients with FA, which makes the diagnosis a clinical challenge. Nevertheless, some specific findings can serve as clues for FA detection. The early identification of these individuals is essential for their proper clinical management.

Key-words: Fanconi anemia; pancytopenia; café-au-lait spots; esophagus; upper extremity deformities, congenital.

RESUMO

Objetivo: Verificar as características clínicas de pacientes com anemia de Fanconi (AF) diagnosticados em um Serviço de Genética Clínica.

Métodos: O estudo incluiu todos os pacientes atendidos no Serviço de Genética Clínica da Universidade Federal de Ciências da Saúde de Porto Alegre e Complexo Hospitalar Santa Casa de Porto Alegre, entre 1975 e 2008, com suspeita clínica de AF submetidos ao estudo de quebras cromossômicas com o uso de diepoxi-butano (DEB) a partir do sangue periférico. Realizou-se uma análise retrospectiva das características clínicas dos pacientes, a partir de um levantamento sistemático dos seus prontuários médicos.

Resultados: A amostra foi composta de 17 pacientes, sendo que em sete o diagnóstico de AF foi confirmado. Os pacientes com AF caracterizaram-se por um fenótipo amplo, oscilando desde um quadro de pancitopenia sem dismorfias

Instituição: Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) e Complexo Hospitalar Santa Casa de Porto Alegre (CHSCPA), Porto Alegre, RS, Brasil

[1]Doutor pelo Programa de Pós-Graduação em Patologia da UFCSPA; Professor da Disciplina de Genética Clínica e do Programa de Pós-Graduação em Patologia da UFCSPA, Porto Alegre, RS, Brasil

[2]Acadêmico do Curso de Medicina da UFCSPA, Porto Alegre, RS, Brasil

[3]Doutorando pelo Programa de Pós-Graduação em Patologia da UFCSPA; Geneticista Clínico do Hospital Materno Infantil Presidente Vargas (HMIPV), Porto Alegre, RS, Brasil

[4]Doutoranda pelo Programa de Pós-Graduação em Patologia da UFCSPA; Professora de Genética Clínica da UFCSPA, Porto Alegre, RS, Brasil

[5]Doutor pelo Programa de Pós-Graduação em Genética e Biologia Molecular da Universidade Federal do Rio Grande do Sul (UFRGS); Professor de Genética Clínica e de Pós-Graduação em Patologia da UFCSPA, Porto Alegre, RS, Brasil

Endereço para correspondência:
Giorgio Adriano Paskulin
Rua Sarmento Leite, 245, sala 403 – Centro
CEP 90050-170 – Porto Alegre/RS
E-mail: paskulin@ufcspa.edu.br

Conflito de interesse: nada a declarar

Recebido em: 1/10/2010
Aprovado em: 20/1/2011

até a presença de múltiplas malformações sem alterações hematológicas. Certos achados, como face triangular, orelhas em abano e manchas café com leite foram frequentes e encontrados apenas nos indivíduos com AF. História de equimoses, hematomas, petéquias, infecções e linfadenopatias foi comum entre os indivíduos desse grupo. Por outro lado, alterações neurológicas foram observadas apenas em pacientes sem AF. Consanguinidade foi verificada em apenas um paciente, que apresentava AF.

Conclusões: Apesar das limitações do estudo, os achados ilustram a grande variabilidade fenotípica observada na AF, o que torna seu diagnóstico clínico um desafio. No entanto, alguns achados específicos podem servir de pistas para sua detecção. A identificação precoce desses indivíduos é fundamental para o seu manejo adequado.

Palavras-chave: anemia de Fanconi; pancitopenia; manchas café-com-leite; esôfago; deformidades congênitas das extremidades superiores.

RESUMEN

Objetivos: Verificar las características clínicas de pacientes con anemia de Fanconi (AF) diagnosticados en un servicio de Genética Clínica.

Métodos: El estudio incluyó a todos los pacientes atendidos en el Servicio de Genética Clínica de UFCSPA / CHSCPA entre 1975 y 2008, con sospecha clínica de AF, sometidos al estudio de rupturas cromosómicas con el uso de diepoxibutano (DEB) a partir de la sangre periférica. Se realizó un análisis retrospectivo de las características clínicas de los pacientes, a partir de un inventario sistemático de sus prontuarios médicos.

Resultados: La muestra fue compuesta por 17 pacientes, siendo que en siete se confirmó el diagnóstico de AF. Los pacientes con AF se caracterizaron por un fenotipo amplio, oscilando desde un cuadro de pancitopenia sin dismorfias hasta presencia de múltiples malformaciones sin alteraciones hematológicas. Ciertos hallazgos, como cara triangular, orejas prominentes y manchas café con leche fueron frecuentes y encontradas solamente en los individuos con AF. Historias de equimosis, hematomas, petequias, infecciones y linfadenopatias fue común entre los individuos de este grupo. Por otra parte, alteraciones neurológicas fueron observadas solamente en pacientes con AF. Consanguinidad fue verificada en solamente un paciente que presentaba AF.

Conclusiones: A pesar de las limitaciones del estudio, nuestros hallazgos muestran la gran variabilidad fenotípica observada en la AF, lo que convierte su diagnóstico clínico en un desafío. Sin embargo, algunos hallazgos específicos pueden servir de pistas para su detección. La identificación precoz de esos individuos es fundamental para su manejo adecuado.

Palabras clave: anemia de Fanconi; pancitopenia; manchas café con leche; esófago; deformidades congénitas de las extremidades superiores.

Introduction

Fanconi anemia (FA - *OMIM* 227650)[1], also known as Fanconi pancytopenia syndrome, is a rare and heterogeneous genetic disease affecting all ethnic groups and found in approximately 1 in 360,000 births[2]. This syndrome was first described in 1927 by Swiss pediatrician Guido Fanconi. The disease was characterized as a rare form of familial aplastic anemia affecting three siblings with short stature, hypogonadism, and skin disorders[2-6].

Currently, FA is considered the most common inherited cause of bone marrow failure. Patients are at increased risk for both hematological and solid tumors (including leukemia, carcinomas, and liver tumors)[7,8]. Many genes can be responsible for this disease, which can be an inherited X-linked disorder and, especially, an autosomal recessive disease; however, all these genes have one thing in common: they do not allow the DNA repair mechanisms work properly[7-9].

Given the importance of identifying these patients and the lack of studies conducted in Brazil mainly focused on their clinical characteristics[10-15], the objective of the present study was to characterize the clinical profile of patients diagnosed with FA seen at a clinical genetics department.

Method

This study included all patients seen at the Clinical Genetics Department of *Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA)/Complexo Hospitalar Santa Casa de Porto Alegre (CHSCPA)* between 1975 and 2008 with clinical suspicion of FA.

Participants were included according to the results of a study of chromosome breakage using diepoxybutane (DEB) based on peripheral blood samples, which is the method used

to diagnose the syndrome. The method was based on the technique described by Auerbach *et al*[16] in 1981, in which cultures of lymphocytes stimulated with phytohemagglutinin of patients and controls (matched for age and sex) were exposed to DEB. In the analysis of the results, we considered the mean chromosome breakage identified by metaphase analyzed both in basal cultures (without DEB) and in those using this alkylating agent, and the number of cells with radial figures. All patients were submitted to the study of karyotype using GTG bands according to the technique modified by Yunis[17]. The results were all reviewed using the International System for Cytogenetic Nomenclature (ISCN) published in 2009[18].

We conducted a retrospective analysis of the patients' clinical characteristics based on a systematic survey of their medical records and completion of a standard clinical protocol. Patients whose medical records contained incomplete clinical description were excluded. This study was approved by the Research Ethics Committee of UFCSPA.

Results

Based on the review of the patients' medical records, we found that 20 patients had undergone the study of chromosome breakage for FA. However, three patients had incomplete medical records and were excluded. Thus, the final sample consisted of 17 patients, and seven of them had the diagnosis of FA confirmed by the test using DEB.

Of the patients with a diagnosis of FA, three were males and four were females. Their age at first evaluation ranged from 2 weeks to 6 years and 6 months (median of 5 years). In the group of patients without a diagnosis of FA, five subjects were males and five were females. Their ages ranged from 3 days to 9 years (median of 1 year and 3 months).

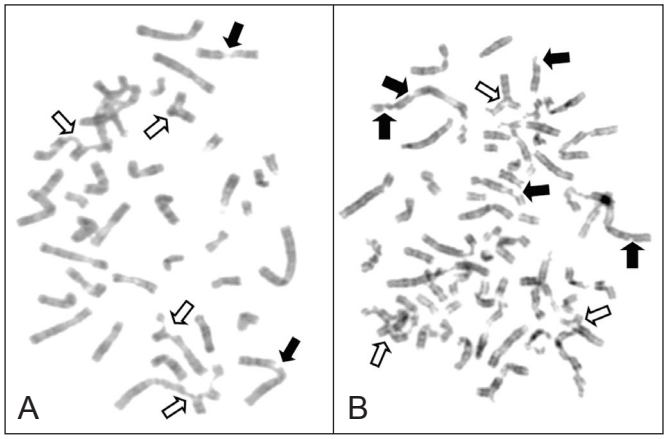

Figure 1 - Karyotype with the induction of chromosome breakage using DEB in patients diagnosed with Fanconi anemia (A and B). Note especially the large number of chromosome breakages (examples indicated by black arrows) and rearrangements (white arrows), especially in "B", a typical finding of the syndrome

As for cytogenetic studies of chromosome breakage, the number of metaphases analyzed using culture was usually 50. The mean number of chromosome breakages per metaphase in baseline cultures (without DEB) was 0.22 (ranging from 0.1 to 0.36) for those without the disease and 0.52 (ranging from 0.41 to 0.64) among patients diagnosed with FA. In relation to cultures with DEB, the means were, respectively, 0.3 (ranging from 0.15 to 0.52) and 4.6 (ranging from 3.9 to 5.2). The mean number of breakages per metaphase in individuals with a diagnosis of FA was 15.3 times higher than in those without FA in cultures with DEB. Radial figures were observed only in patients with FA (mean of 15 figures per case – ranging from 10 to 21) (Figure 1). According to the study of karyotype using GTG bands, we found two patients with chromosomal abnormalities in the group without FA: one case of trisomy 9 mosaicism syndrome and one case of a reciprocal translocation apparently balanced between chromosomes 6 and 9.

The clinical characteristics of all patients are described in Tables 1 and 2. Consanguinity was identified in only one patient (14%) who had been diagnosed with FA (Figure 2). Family history of clinical findings observed in FA was detected mainly among individuals with FA (57%). These findings consisted of café au lait spots (14%), hand abnormality (14%), anemia (14%), and cardiac malformation (14%). The family members with these findings were, respectively, a brother in 50% of cases, the mother in 25%, and an aunt in 25%. Only one patient without the syndrome (10%) had family history of congenital heart disease (a cousin of this patient had the same malformation).

Regarding the phenotype of patients with FA, one of them (14%) had no dysmorphic disorders; presenting only with blood problems. Triangular face (29%), protuberant ears (29%), and café au lait spots (43%) were relatively frequent findings, being found only among individuals with the syndrome. Radial changes were found in five patients (71%) and consisted of low-placed thumb (43%), thumb hypoplasia (14%), thumb agenesis (14%), and long thumb (14%). Involvement was usually bilateral and asymmetrical (Tables 1and 2).

Findings observed only among subjects without FA consisted mainly of neurological disorders such as neuropsychomotor delay (60%), central nervous system abnormalities

Table 1 - Clinical findings in the patients, grouped according to whether there was or not diagnosis of Fanconi anemia (Part 1).

Findings	Fanconi Anemia		TOTAL
	Yes n=7	No n=10	n=17
Without dysmorphism	1	2	3
Short stature	1	3	4
Neurological			
Developmental delay	7.	6.9	6
Hypotonia	-	3	3
Delayed speech &	2.7	4.9	6
Craniofacial			
Microcephaly	2	2	4
Triangular face	2	-	2
Ptosis	-	1	1
Epicanthic fold	2	5	7
Hypertelorism	1	-	1
Strabismus	1	2	3
Broad nasal root	2	1	3
Anteverted nostrils	1	1	2
Hypoplastic nostrils	1	-	1
Cleft lip	-	1	1
High palate	-	3	3
Micrognathia	1	1	2
Preauricular pit	-	1	1
Microtia	1	-	1
Dysplastic ears	-	2	2
Prominent ears	2	-	2
Retroverted ear	-	1	1
Low implanted ear	-	1	1
Auditory canal stenosis	1	-	1
Prominent occiput	1	1	2
Neck/Chest			
Congenital torticollis	-	1	1
Pectus excavatum	-	1	1
Pectus carinatum	-	1	1
Abdomen			
Inguinal hernia	1	-	1
Upper Limbs			
Single palmar crease	1	2	3
Clinodactyly of fifth finger	2	2	4
Radial anomalies	5	6	11
Dysplastic nails	1	1	2
Pelvis			
Penile chordee	1	-	1
Hypospadias	-	1	1
Cryptorchidism	-	2	2
Lower limbs			
Lymphedema	1	-	1
Prominent calcaneus	-	1	1
Syndactyly between 2nd and 3rd fingers	-	2	2
Skin			
Café au lait spots	3	-	3
Hyperpigmentation of the neck	1	-	1
Cutis marmorata	-	1	1

& evaluated according to patient's age.

Table 2 - Abnormalities observed in the patients with and without a diagnosis of Fanconi anemia detected by laboratory tests

Findings	Fanconi Anemia		TOTAL
	Yes n=7	No n=10	n=17
Neurological			
Swallowing disorder	-	3	3
Porencephalic cyst	-	1	1
Ventricular dilatation	-	1	1
Periventricular leukomalacia	-	2	2
Craniofacial			
Hearing impairment	-	3	3
Neck/Chest			
Tracheomalacia	1	1	2
Esophageal atresia	1	1	2
Rib deformity	1	-	1
Congenital heart disease	-	3	3
Vertebral deformities	-	1	1
Scoliosis	-	3	3
Abdomen			
Renal anomaly	1	2	3
Upper Limbs			
Radial hypoplasia	-	1	1
Radial agenesis	-	1	1
Shortening of the proximal phalanges	-	1	1
Thumb hypoplasia	1	3	4
Triphalangeal thumb	-	1	1
Hematologic			
Pancytopenia	3	2	5
Anemia	2	3	5
Thrombocytopenia	1	1	2

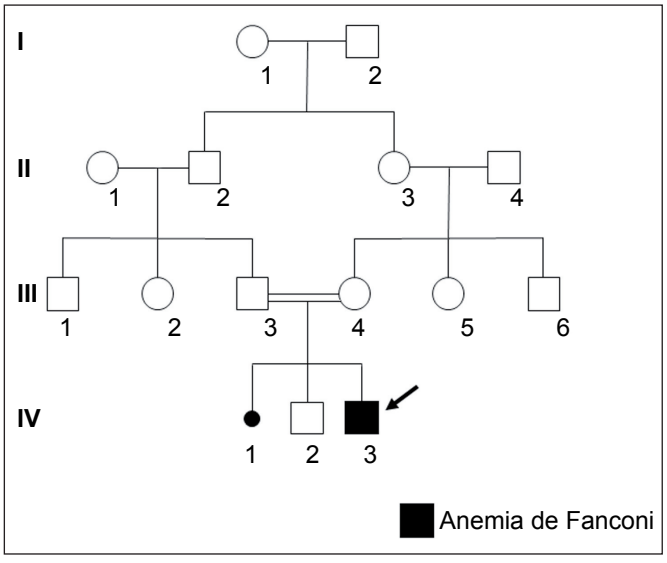

Figure 2 - Ideogram of the family of a patient diagnosed with FA (individual IV-3). Note mainly the consanguinity between their parents (III-3 and III-4), which correlates with the autosomal recessive form of FA.

(40%), hypotonia (30%), and swallowing disorders (30%). Other changes found only in this group included congenital heart disease (30%) and scoliosis (30%). Radial abnormalities were found in six patients without FA (60%) and consisted of thumb hypoplasia (30%), preaxial polydactyly (30%), radial hypoplasia (10%), radial agenesis (10%), low-placed thumb (10%), triphalangeal thumb (10%), sessile thumb (10%), and thumb agenesis (10%) (Tables 1 and 2).

Hematological changes were found in both groups (Table 2). In relation to clinical events, they were much more frequent in individuals with FA. These events consisted of a history of ecchymosis, bruises, and petechiae (42%); infections (42%); lymphadenopathy (28%); hepatosplenomegaly (14%), and diarrhea (14%). Intercurrent diseases observed in the group without a diagnosis of FA included a history of bleeding (10%) and hepatosplenomegaly (10%). Only one patient with FA had died from an infection.

Discussion

When pediatrician Guido Fanconi first described FA, he could not imagine that this disease would eventually reveal an important mechanism of cellular defense against genetic instability[19]. Although it is a gene disease instead of being a chromosomal disease, the diagnosis of FA is usually confirmed by a specific study of karyotype. A differential technique with clastogenic substances, such as DEB or mitomycin C (MMC), is used to promote DNA damage, breakage and rearrangement of chromosomes and cell death. This is very important because, although individuals with the syndrome show a spontaneous predisposition to chromosome breakage, in some cases the baseline cultures (without these agents) may show normal results (which are considered false negatives). The DEB test is considered the gold standard for diagnosis of FA (it is more sensitive than MMC). Results are compared with those of a normal control group, especially matched for sex and age. At least 25 metaphases per culture are microscopically analyzed. Chromosomes of patients with FA tend to spontaneously rupture and break more easily in the presence of the substances used. They even regroup forming radial figures or letters (Figure 1). These figures are considered to be triradial when there are two breakages and tetraradial when there are three breakages. In the study of karyotype, the number, the type and the distribution of the chromosome breakages are detected in each cell[2,10,20-23]. The degree of sensitivity to DEB or MMC is not correlated with neither the phenotype nor the severity of the disease. Furthermore, it is important to be aware that individuals that are heterozygous for the FA cannot be detected using this DEB/MMC test[9]. Other interesting aspect is related to the sites where chromosome breakage occurs. Some studies, such as Schoder *et al*[24], have shown that these sites have an important relationship with fragile sites, which are chromosomal regions that may have a high incidence of gaps and breakages on metaphase chromosomes of healthy individuals.

However, the effectiveness of this test has been questioned, since a negative result has been found in some cases diagnosed using the molecular analysis[10]. Furthermore, patients with mosaicism for FA (who have a genetic constitution with more than one type of cell line, usually a normal line and a line modified for the syndrome) may have a false-negative result. Thus, in cases where blood testing was normal and diagnostic doubt persists, it is important to analyze another tissue with the breakage induction, usually fibroblasts[2,9,25]. Therefore, we cannot assume that all our patients with negative results for FA will not have the syndrome.

There are at least 13 genes involved in the presentation of the FA phenotype, which correspond to complementation groups ranging from A to N (*FANCA-N*). All these genes are located in very different regions, involving both autosome and sex (X chromosome) chromosomes[9,19,25,26]. In addition, several different mutations have been identified in each one of these genes, which makes the disease even more genetically heterogeneous. The genes *BRCA1* (OMIM 113705)[1] and *BRCA2* (OMIM 600185)[1] are also associated with the abnormal DNA repair pathway in FA, and it has been recently found that *FANCD1* and *BRCA2* genes are actually the same gene[4,5,7,11]. Among the complementation groups, the most often mentioned is A (*FANCA*), reported in 57 to 65% of the cases[11]. Despite major advances in the past decades regarding the molecular mechanisms involved in FA, a genotype-phenotype correlation has not been well defined. Phenotypic variations have been found even in individuals of the same family and in monozygotic twins[26,27].

Thus, the great clinical variability of FA makes it difficult to establish its clinical diagnosis[27]. This phenomenon could be observed among the individuals investigated in the present study, whose phenotype ranged from patients with isolated pancytopenia to patients with multiple malformations and absence of hematological disorders. Major congenital malformations have been reported in

approximately two thirds of the patients with FA and can affect almost any organ or system. Conversely, one third of the patients did not present the same abnormalities[27]. In these patients, the diagnosis is usually performed only after the onset of symptoms of hematologic dysfunction, which usually start at around 7 years of age, ranging from birth to 31 years[2,27].

Nevertheless, there are some clinical signs that may help to establish the diagnosis of FA. For example, findings observed only among patients with FA included some craniofacial abnormalities (such as triangular face and protruding ears) and café au lait spots. Craniofacial abnormalities have been described in the literature in 25% of cases of FA. Other abnormalities include epicanthic folds, strabismus, hypertelorism, ear canal stenosis, and microtia. These findings were also evident in our patients[2,27]. Although craniofacial abnormalities are subtle, some authors claim that they might enable the clinical identification of individuals with FA[25]. Skin abnormalities, in turn, are described in the literature in 45-60% of cases, and are characterized mainly, as observed in our sample, by café au lait spots and localized or usually generalized hyperpigmentation[2,23].

Radial abnormalities, a classic finding of FA, are described in about 50% of children and mainly consist of absence or hypoplasia of the thumb, bifid or supernumerary thumbs, and absence or hypoplasia of the radius[2,6,25]. These abnormalities were present in 71% of the patients in the present study. Radial abnormalities may be unilateral or bilateral, and even those who have bilateral abnormalities usually present with a certain asymmetry, with their limbs showing different anomalies[27]. Radial anomalies, along with hematologic dysfunctions, were frequent in both groups of our study (with and without FA), and this finding may be related to the fact that it represents the main reasons that lead to suspicion o FA[3,5,6,11].

Conversely, neurological disorders, such as hypotonia, neuropsychomotor development delay, swallowing disorders, and central nervous system abnormalities, are uncommon in FA[2] and were only found in individuals without this diagnosis. About 5% of patients with FA may also have serious gastrointestinal malformations of various degrees of severity, which may require early surgical treatment[2,25]. Abnormalities of the esophagus, which was found in one of our patients, are considered unusual[27]. In addition, FA has been rarely seen in individuals with esophageal atresia. However, when there is esophageal atresia in combination with other findings, this abnormality may mimic the phenotype of the VATER/VACTERL association (acronym for vertebral anomalies, imperforate anus, congenital heart disease, esophageal atresia with tracheoesophageal fistula, renal and limb anomalies) (OMIM 192350)[1], an important differential diagnosis of FA[28].

FA patients also usually show changes in growth parameters, such as height, weight and/or head circumference below the fifth percentile[27]. In our sample, we found patients with short height (n=1) and microcephaly (n=2). Other less frequent abnormalities, such as cardiac and renal disorders[2], were not observed in patients with FA in our study.

History of consanguinity between parents was found only in one patient with FA (Figure 2), and it is related to the etiology of the syndrome, since, as previously mentioned, most cases segregate in an autosomal recessive form. Regarding family history, four patients with FA had relatives with abnormalities belonging to the spectrum of the syndrome, and these abnormalities were observed only in one individual of the other group. It was not possible to specify the relevance of this finding; however, this could indicate the presence of more individuals affected in the same family. Nevertheless, further clinical data and additional diagnostic tests would be necessary to confirm this hypothesis. Currently, there is a consensus in the literature that, due to lack of FA phenotype concordance among affected siblings, all siblings of a patient with FA should be investigated for the syndrome[27].

Another important aspect of FA is the low life expectancy of those affected by this disease (20 years on average), and the probability of survival over 50 years is almost zero[3,6]. This is mainly due to aplastic anemia and the higher likelihood of these patients to develop acute myeloid leukemia, myelodysplastic syndrome, or solid tumors (especially after 20 years of age)[2-6,21]. History of ecchymosis, bruises, petechiae, lymphadenopathy events, and infections were common among our patients with FA. With the advances in the treatment of hematologic disorders of individuals with FA, infections have emerged as the main clinical complication, even after the development of new antibiotics[25]. Many children with FA eventually die because of bacterial and fungal infections, and neutropenic infections are usually poorly tolerated and typically not cured only with antibiotics[25], as it happened to one of the patients in our sample. We did not identify any cases of hematologic or solid tumor in our study.

The frequency of heterozygous individuals is considered to be 1/300 people in Europe and the United States. However,

there are ethnic groups in which this rate is higher, such as in communities of Ashkenazi Jews and African descendants of Dutch, reaching 1/100 individuals[2,4,5,27]. Currently, the risk of neoplasias detected in FA may extend even to carriers (heterozygous), such as the parents of patients with the syndrome. In the present study, we did not demonstrate any case of relative with neoplasia.

The differential diagnosis of FA should include the VATER/VACTERL association, besides the Holt-Oram syndrome (OMIM 142900)[1] and the syndrome of thrombocytopenia and radial agenesis (TAR) (OMIM 274000)[1] mainly due to the radial abnormalities. Other conditions to be considered include the Diamond-Blackfan anemia (OMIM 105650)[1] (especially because of the hematological picture), neurofibromatosis type 1 (OMIM 162200) [1] (because of café au lait spots), and other chromosomal instability syndromes such as the Bloom syndrome (OMIM 210900)[1] and the ataxia-telangiectasia syndrome (OMIM 208900)[1]. However, none of the instability syndromes shows karyotype abnormality when the karyotype is processed using DEB/MMC[2,4,5,27].

Early identification of individuals with FA is critical because it allows an adequate control of the patient's hematologic disorder, performance of surgical treatments to correct major congenital malformations before thrombocytopenia, genetic counseling for the family regarding risks in future pregnancies, and possibility of prenatal diagnosis and presymptomatic identification of affected siblings or pregnancies whose fetuses are possible donors of hematopoietic stem cells to an affected sibling[2,27]. Moreover, the diagnosis allows for appropriate treatment of patients because individuals with FA may experience greater toxicity if they receive a standard dose of chemotherapy regimens before transplantation of hematopoietic stem cells[29,30]. Since there is late onset of pancytopenia, the diagnosis of FA should be considered in all children with characteristic dysmorphic findings, even in the absence of hematological abnormalities[6].

Despite the small sample size, which may be a result of non-referral of patients with FA to investigation and genetic counseling, and only the use of the technique of lymphocyte culture with DEB, without complementary tests in those patients who did not have increased number of chromosome breakages, our findings illustrate the great phenotypic variability observed in FA, which makes its clinical diagnosis a challenge. However, specific findings, such as radial alterations and café au lait spots, should remind us of the possibility of this diagnosis. FA is a genetic disease with predisposition to cancer that requires a multidisciplinary follow-up so that appropriate clinical management of patients and their families is achieved.

References

1. Online Mendelian Inheritance in Man, OMIM (TM) [homepage on the Internet]. Baltimore e Bethesda: BeMcKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University and National Center for Biotechnology Information, National Library of Medicine [cited 2010 Sept 5]. Available from: http://www.ncbi.nlm.nih.gov/omim/
2. Sagaseta IM, Molina J, Lezáun I, Valiente A, Durán G. Anemia de Fanconi. Consideraciones actuales. Anales Sis San Navarra 2003;26:63-78.
3. Joenje H, Patel KJ. The emerging genetic and molecular basis of Fanconi anaemia. Nat Rev Genet 2001;2:446-57.
4. Tischkowitz MD, Hodgson SV. Fanconi anaemia. J Med Genet 2003; 40:1-10.
5. Chen H. Atlas of genetic diagnosis and counseling. New Jersey: Humana Press; 2006.
6. Jones K. Smith's recognizable patterns of human malformation. 6th ed. Philadelphia: Elsevier; 2006.
7. Kennedy RD, D'Andrea AD. DNA repair pathways in clinical practice: lessons from pediatric cancer susceptibility syndromes. J Clin Oncol 2006;24:3799-808.
8. Tootian S, Mahjoubi F, Rahnama M, Hormozian F, Mortezapour F, Razazian F *et al*. Cytogenetic investigation in Iranian patients suspected with Fanconi anemia. J Pediatr Hematol Oncol 2006;28:834-6.
9. Taniguchi T. Fanconi Anemia. In: Pagon RA, Bird TC, Dolan CR, Stephens K, editors. GeneReviews. Seattle (WA): University of Washington; 1993.
10. Lima CS, Lourenço GJ, Rodriguez DE, Zocca M, Bertuzzo CS. Cytogenetic and molecular diagnosis of Fanconi anemia. Rev Bras Hematol Hemoter 2003;25:191-2.
11. Magdalena N, Pilonetto DV, Bitencourt MA, Pereira NF, Ribeiro RC, Jeng M *et al*. Frequency of Fanconi anemia in Brazil and efficacy of screening for the *FANCA* 3788-3790del mutation. Braz J Med Biol Res 2005;38:669-73.
12. Pasquini R, Neto JZ, Medeiros CR, Bitencourt MA, Bonfim CM, Moreira VA *et al*. Carcinoma de células escamosas em língua pós-transplante de medula óssea por Anemia de Fanconi. Rev Bras Hematol Hemoter 2003;25:239-46.
13. Rodriguez DE, Lima CS, Lourenço GJ, Figueiredo ME, Carneiro JD, Tone LG *et al*. Molecular analysis of the most prevalent mutations of the FANCA and FANCC genes in Brazilian patients with Fanconi anaemia. Genet Mol Biol 2005;28:205-9.
14. Horta HL, Guimarães FF, Rocha LO, Guimarães RE, Valadares ER. Carcinoma de células escamosas da hipofaringe em mulher jovem com anemia de Fanconi. Rev Bras Otorrinolaringol 2006;72:845-8.
15. Medeiros CR, Bitencourt MA, Zanis-Neto J, Maluf EC, Carvalho DS, Bonfim CS *et al*. Allogeneic hematopoietic stem cell transplantation from an alternative stem cell source in Fanconi anemia patients: analysis of 47 patients from a single institution. Braz J Med Biol Res 2006;39:1297-304.
16. Auerbach AD. Fanconi anemia and its diagnosis. Mutat Res 2009;668:4-10.
17. Yunis JJ. New chromosome techniques in the study of human neoplasia. Hum Pathol. 1981;12:540-9.

18. Shaffer LG, Slovak ML, Campbell LJ. ISCN: An International System for Human Cytogenetic Nomenclature. Basel: S. Karger; 2009.
19. de Winter JP, Joenje H. The genetic and molecular basis of Fanconi anemia. Mutat Res 2009;668:11-9.
20. Brown MG, Lawce HJ. Peripheral blood cytogenetic methods. In: Barch MJ, Knutsen T, Spurbeck J, editors. The AGT cytogenetics laboratory manual. 3rd ed. Philadelphia: Lippincott-Raven; 1997. p. 163-7.
21. Zhang XX. Chromossome instability. In: Gersen SL, Keagle MB. The principles of clinical cytogenetics. 2nd ed. New Jersey: Humana Press; 2005. p. 350-1.
22. Ottoni FA, Froes GC, Pimenta MR, Vale EC. Do you know this syndrome? An Bras Dermatol 2006;81:487-9.
23. Korgaonkar S, Ghosh K, Vundinti BR. Clinical, genetic and cytogenetic study of Fanconi anemia in an Indian population. Hematology 2010; 15:58-62.
24. Schoder C, Liehr T, Velleuer E, Wilhelm K, Blaurock N, Weise A *et al*. New aspects on chromosomal instability: chromosomal break-points in Fanconi anemia patients co-localize on the molecular level with fragile sites. Int J Oncol 2010;36:307-12.
25. Green AM, Kupfer GM. Fanconi anemia. Hematol Oncol Clin North Am 2009;23:193-214.
26. Neveling K, Endt D, Hoehn H, Schindler D. Genotype-phenotype correlations in Fanconi anemia. Mutat Res 2009;668:73-91.
27. Auerbach AD, Adler B, Chaganti RS. Prenatal and postnatal diagnosis and carrier detection of Fanconi anemia by a cytogenetic method. Pediatrics 1981;67:128-35.
28. Stoll C, Alembik Y, Dott B, Roth MP. Associated malformations in patients with esophageal atresia. Eur J Med Genet 2009;52:287-90.
29. Dufour C, Svahn J. Fanconi anemia: new strategies. Bone Marrow Transplant 2008;41 (Suppl 2):S90-5.
30. Pinto FO, Leblanc T, Chamousset D, Le Roux G, Brethon B, Cassinat B *et al*. Diagnosis of Fanconi anemia in patients with bone marrow failure. Haematologica 2009;94:487-95.