

Clinical features and diagnosis of Fanconi's anemia

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Clinical suspicion of Fanconi's anemia

When Fanconi described a family with three children with birth defects and aplastic anemia (AA), he made the first clinical observation of what is now clearly a hematological syndrome (Fanconi, 1927). After a few more such families were recognized by others, Fanconi's name was assigned to this phenotype, which is now called Fanconi's anemia (abbreviated FA). In many ways, we have come a long way since then, with the knowledge that there may be at least eight genes responsible for this autosomal recessive condition (Joenje et al., 1997), the cloning of three and mapping of a fourth gene (de Winter et al., 1998; Lo Ten Foe et al., 1996; Strathdee et al., 1992*ab*; The Fanconi Anaemia/Breast Cancer Consortium, 1996; Whitney et al., 1995), and substantial insights into the evolution and treatment of many of the complications of this disorder (see Alter and Young, 1998; Young and Alter, 1994 for recent reviews). However, we still do not always know who to suspect of this condition, precisely how to definitively diagnose or exclude it, how to predict the course of a specific patient, and how to cure or even treat many patients. Given many caveats with regard to biased and possibly incorrect ascertainment, more than 1000 cases of FA have been reported in the literature, with a male:female ratio of 1.3:1. The average age at diagnosis is 7.8 years for males, and 8.8 years for females, with a range from birth to adults. Approximately 5% were diagnosed in the first year of life, and 10% were diagnosed at 16 years of age or more.

The first major problem in the diagnosis of FA is the selection of patients who should be tested. There is a high index of suspicion in children with AA who have physical abnormalities similar to those described in the early literature; this aspect has clearly skewed both the testing and the reporting of FA. Although the incidence of those anomalies is undoubtedly less than the >75% ascertained from literature reports (Alter and Young, 1998), the true figure will not be clear until all genes are cloned, and population screening can be performed. As a minimum, it is important that patients with characteristic birth defects be

Table 17.1. Physical abnormalities in Fanconi's anemia

Abnormality	All patients (%)	<1 year at diagnosis (%)	>16 years at diagnosis (%)
Skin	60	35	66
Short stature	57	50	59
Upper-limb anomalies	48	68	37
Hypogonads, male	37	42	47
Hypogonads, female	3	19	5
Head	27	38	16
Eyes	26	33	22
Renal	23	45	19
Birth weight <2500 g	12	50	7
Developmental delay	13	5	7
Lower limbs	8	15	4
Ears	10	25	10
Increased reflexes	7	3	3
Other skeletal anomalies	6	8	13
Cardiopulmonary	6	18	3
Gastrointestinal	4	30	0
Other anomalies	5	3	2
None, or not reported	20	15	20
Short stature only	1	0	0
Skin only	3	0	3
Short stature and skin only	4	3	5
Short stature and/or skin	8	3	9
Number of patients	955	40	91
Male:female	1.3:1	1.5:1	1.2:1

Notes:

Data represent percentage of patients with the abnormality. The proportions are underestimates, since some reports did not provide physical descriptions. Many patients had multiple anomalies. From Alter and Young, 1998.

identified as FA patients from the outset, for early treatment, and for genetic counseling with regard to subsequent pregnancies. Thus, any of the anomalies summarized in Table 17.1 should be triggers for consideration of the diagnosis of FA. As shown, there are age-related differences in the observation of some of the findings, such as stature and pigmentation. The most frequent abnormalities overall are short stature, hyperpigmented skin, café au lait spots or hypopigmented areas, thumb and radial deformities, microcephaly, microphthalmia, structural renal anomalies, and hypogonadism. Details of all the physical

findings that have been reported are provided elsewhere (Alter and Young, 1998; Young and Alter, 1994). The incidence of FA in the absence of major anomalies may emerge from the International Fanconi Anemia Registry (IFAR, Butturini et al., 1994), but the IFAR is biased by the fact that many patients are only diagnosed after they develop AA or even leukemia, and thus the IFAR data may not indicate the true incidence of mild or asymptomatic homozygous FA. Studies of siblings suggest that 25% of patients lack major anomalies (Glanz and Fraser, 1982), while a review of IFAR patients found that 30% lacked congenital malformations, although minor malformations and particularly short stature, microsomy, skin pigmentation, and microphthalmia were almost as frequent in this group of patients as in those with significant birth defects (Giampietro et al., 1997).

The next group to be considered at risk of FA are all patients with AA, irrespective of their physical appearance. Most, although still not all (!), pediatric hematologists include testing for FA in the initial work-up of all children with newly diagnosed 'acquired' aplastic anemia. Were this to become a universal procedure for AA patients of all ages, the frequency of FA as the cause of AA could be ascertained. Reviews from two pediatric centers in the era before modern FA testing suggested that at least 25% of children with AA in fact had FA, but the diagnosis of FA was based on clinical phenotype, and thus those figures were clearly underestimates (Alter et al., 1978; Windass et al., 1987). The frequency of FA homozygotes has been estimated (without hard data) at one to three per million (Joenje et al., 1995). A 13-year study of childhood AA in the north of England suggested an annual incidence of acquired AA of 2 per million, and of AA due to FA of 1.4 per million; 42% of 24 children with AA had FA (Tweddle and Reid, 1996). There are no meaningful adult data, and adults with undiagnosed FA are usually considered to have acquired AA and are treated accordingly (and incorrectly). There are recent reports of adults diagnosed in their thirties to fifties (Kwee et al., 1997; Liu et al., 1991; Zatterale et al., 1995), and other cases known anecdotally to this author. Although the IFAR suggests a cumulative risk of AA of 98% in patients with FA (Butturini et al., 1994), the IFAR cannot provide the obverse figure, which is the frequency of FA as the cause of AA.

Diagnosis of FA

How can the diagnosis of FA be made at this time? The 'gold standard' for the diagnosis of FA was developed following the early observations of increased chromosomal fragility (Schroeder et al., 1964), which is enhanced in the presence of deoxyribonucleic acid (DNA) clastogenic agents such as mitomycin C (MMC) or diepoxybutane (DEB) (Auerbach et al., 1981; Cervenka et al., 1981). This method involves analysis of chromosome breakage in metaphase preparations of phytohemagglutinin-stimulated cultured peripheral blood lymphocytes to which the DNA crosslinker has been added for a specific time period. FA cells usually show

a high frequency of breaks, gaps, rearrangements, exchanges, and endoreduplications. Cultured skin fibroblasts may also be used for this test. Diagnosis is fairly certain when chromosome breakage is positive with MMC or DEB, but a negative breakage test may not exclude FA.

Until recently, the chromosome breakage test was considered to be diagnostic, specific, and relatively sensitive. Approximately 10% of patients were classified as 'clonal', however, because of the presence of only a small proportion of cells with chromosome breaks, in a background of cells lacking breaks (Auerbach et al., 1989). Explanations for this phenomenon can now be evoked, and demonstrated at the molecular level. In compound heterozygotes for different mutations of the same gene, intragenic rearrangements or other molecular events, such as gene conversion in rapidly dividing hemopoietic cells, may lead to *in vivo* gene correction in clones of cells. This may result in a 'false-negative' test for chromosome breakage, such as was initially observed for one of two FA brothers (Dokal et al., 1996), and subsequently reported for seven additional mosaic patients (Lo Ten Foe et al., 1997). Since DNA studies (see below and Chapter 18) now permit definitive diagnosis in some cases, the 'gold standard' has been proven to be tarnished.

A different approach has been taken by several groups who examined cell cycle kinetics in FA. Progression through the cell cycle was delayed, and the proportion of lymphocytes arrested at G₂/M was increased in most FA patients after culture in nitrogen mustard (Berger et al., 1993); in that study the only negative results were in three FA patients with myelodysplasia or leukemia. Another group examined the cell cycle without adding a DNA crosslinker, and found nondiagnostic results only in three FA patients with leukemia (Seyschab et al., 1995). They also identified five cases in which the cell cycle delay was apparent, but classic chromosome breakage studies were normal, and suggested that those patients had atypical or mild FA disease which would have been missed by standard tests. Our own group has performed cell cycle studies using a nitrogen mustard dose/response curve, and found an abnormal result in a patient with normal DEB and MMC breakage studies, later found to be a mosaic, as discussed above (Arkin et al., 1993; S. Arkin, B. P. Alter and J. M. Lipton unpublished). All known FA patients had abnormal results in this test, and nonFA AA patients, such as those with acquired AA or dyskeratosis congenita, had normal results.

The molecular genetics of FA will be discussed in detail in Chapter 18, but a very brief summary cannot be omitted here, since this is the future of accurate diagnosis of FA. The genetic heterogeneity of FA was suggested by complementation analyses as early as 1980 (Yoshida, 1980). In those experiments, cells from various FA patients were fused and examined for correction of chromosome breakage. Cells which corrected came from patients who belonged to different complementation groups, while failure to correct indicated that they were from the same group. These studies were extensively expanded by Joenje and his colleagues, who have now found at least eight different groups (Joenje et al., 1997). The gene for FA

group C, now called *FANCC*, was cloned in 1992, and mapped to 9q22.3 (Strathdee et al., 1992*ab*). The FA group A gene, *FANCA*, cloned in 1996, maps to 16q24.3 (Lo Ten Foe et al., 1996; The Fanconi Anaemia/Breast Cancer Consortium, 1996). *FANCD* has been mapped to 3p22–26 (Whitney et al., 1995), but is not yet cloned. The third cloned gene, *FANCG*, was recently mapped to 9p13, and codes for XRCC9 (de Winter et al., 1998). The gene products, their cellular localization, and possible functions will be discussed elsewhere (Chapter 18).

Molecular methods are now widely and rapidly employed to identify the genetic defects in specific patients. Complementation analysis may be used to assign a patient to a specific group, and to determine population frequencies and founder effects (Joenje, 1996); for example, the high incidence of group A in Italy, Germany, Saudi Arabia, and in South African Afrikaans (The Fanconi Anaemia/Breast Cancer Consortium, 1996), the association of group C with Germany (Joenje, 1996), and a specific group C mutation at IVS4 A→T with Ashkenazi Jews (Whitney et al., 1994). Results in North America indicate 69% group A, 18% C, 4% D, and 9% B or E (Jakobs et al., 1997). Screening for specific mutations can be done with various molecular techniques, such as Southern blotting, oligonucleotide hybridization, restriction site assays, amplification refractory mutation, chemical cleavage mismatch analysis, and single-strand conformational polymorphism. Positive results from these tests, with exclusions of silent polymorphisms, serve to make a definite diagnosis of FA in a candidate patient. However, negative results do not exclude FA, since the mutation may not have been found by the technology that was employed. Nevertheless, when all of the genes and their mutations are elucidated, this approach should become the new 'gold standard'. In populations with a unique mutation, such as the IVS4 A→T in Ashkenazi Jews, the carrier frequency can be determined, and previously undiagnosed homozygotes identified. For example, carriers were shown to comprise 1% of Ashkenazi Jews in New York, and 0% of Israeli Iraqi Jews (Verlander et al., 1995). Molecular studies will also be invaluable for prenatal diagnosis in families in which the specific mutation is known, including those identified by population screening, rather than through a propositus.

Genotype/phenotype correlations are available so far only within the group C population studied in the IFAR (Gillio et al., 1997). Approximately 15% of the close to 400 patients screened belonged to group C. The largest number of major congenital malformations was found in those with the IVS4 A→T mutation, with the next in frequency in those with a mutation in exon 14, and the fewest malformations in those with a mutation in exon 1 (322delG). Those with mutations in exon 14 or IVS4 also had an earlier onset of hematological disease and a shorter median survival than the exon 1 patients. NonC patients, presumably mostly mutant in *FAA*, were similar to the exon 1 patients. Leukemia occurred earlier in the exon 14 and IVS4 patients than in the exon 1 group. Sensitivity to DEB-induced chromosome breakage had an unexplained negative correlation with

genotype severity (e.g., the largest number of breaks per cell was seen in those with exon 1 mutations).

Prenatal diagnosis of FA can be done by analysis of clastogen-induced chromosome breakage in cultured fibroblasts, or in fetal lymphocytes obtained by percutaneous umbilical blood sampling (Auerbach and Alter, 1989). DNA-based diagnoses can be used with the methods already outlined, in situations in which the mutation has been identified in a proband, or in the carrier parents. These diagnoses will be more reliable, and more rapid than the cell-culture-dependent methods used formerly.

Hematological manifestations

Peripheral blood manifestations of FA encompass the entire spectrum from normal to macrocytosis and/or increased fetal hemoglobin (Hb F) levels, to thrombocytopenia, neutropenia, and/or anemia, to trilineage pancytopenia. The blood smear may have large red cells, anisocytosis, mild poikilocytosis, and cytopenias. Red cell mean cell volume (MCV) and Hb F levels may be higher in FA than in acquired AA, but this distinction cannot be relied upon for individual cases. However, increased MCV or Hb F levels may be an early indicator of FA in an asymptomatic sibling of a proband. Conversely, the MCV may be inappropriately normal in the presence of concomitant iron deficiency or thalassemia trait (Alter, 1998). Bone marrow examination may reveal evolving aplasia, with progressively decreasing cellularity, loss of normal myeloid hemopoietic elements, and relatively increased numbers of lymphocytes, reticulum cells, mast cells, and plasma cells. We attempted to classify FA patients according to their hematological status before any genotype information was available, in order to correlate *in vitro* culture data with the *in vivo* condition (Table 17.2; Alter et al., 1991b). This classification scheme may be useful with regard to correlation of the timing of the decline in hematological class with genotype. The only genotype/phenotype correlations for hematological status are limited to those cited already from the IFAR.

It is fair to state that the major problem for FA patients who have been diagnosed to date is the risk of AA. The only available 'cure' at this time is bone marrow transplantation, preferably from an HLA-matched sibling. For those for whom transplant is not currently an option, treatment possibilities include androgens and steroids ('standard of care'), to which there is a 50–75% response rate (Alter and Young, 1998), with the most frequent responses including a rise in hemoglobin, followed by a possible increase in platelet count; neutrophil improvement occurs less often. An alternative that will improve the white cell count in essentially all patients is the use of granulocyte colony-stimulating factor (G-CSF), but platelet and hemoglobin responses to this agent are usually not dramatic (Rackoff et al., 1996). Treatment modalities are examined in detail

Table 17.2. Clinical classification of Fanconi's anemia

Group	Transfusions	Androgen or cytokine treatment	Status
1	Yes	No	Severe aplastic anemia, failed or never received androgens
2	Yes	Yes	Severe aplastic anemia, currently on but not responding to androgens
3	No	Yes	Previously severe or moderate aplasia, responding to androgens or cytokines
4	No	No	Severe or moderate aplastic anemia, needs treatment
5	No	No	Stable, with some sign of marrow failure (e.g., mild anemia, neutropenia, thrombocytopenia, high red cell mean cell volume, high fetal hemoglobin)
6	No	No	Normal hematology \pm normal fetal hemoglobin

Note:

From Alter et al., 1991*b*.

in Chapter 19, and gene therapy in Chapter 20. It must be pointed out that there are potentially serious side-effects to most of the treatments, such as the risk of secondary malignancies following bone marrow transplant or gene therapy, of liver tumors from androgens, and risk of leukemia from G-CSF.

Leukemia

Leukemia is reported to occur in approximately 10% of FA patients in the literature (Alter, 1996) at a mean age of 14 years, with a male:female ratio of 1.3:1 (Table 17.3). Leukemia was the presenting problem for 20 of the 84 patients with FA and leukemia. The major type was acute myeloid leukemia (AML), with 30 myeloblastic, 20 myelomonocytic, nine monocytic, seven erythroleukemia, six unspecified, six 'nonlymphocytic', one megakaryoblastic, and two chronic myelomonocytic (which may be classified under myelodysplasia, see later). Only three were reported to be acute lymphoblastic, although this is the type usually seen in children without FA. Five patients had coincidental liver tumors (see below), one an astrocytoma, and one a retinoblastoma. Only three long-term remissions were reported, for 2, 8, and >10 years. Chemotherapy was problematic, since the therapeutic index between toxicity to leukemic cells and sensitivity of normal

Table 17.3. Complications in Fanconi's anemia

	Leukemia	MDS	Cancer	Liver disease
Number of patients	84	68	47	37
Percentage of total	9%	7%	5%	4%
Male:female	1.3:1	0.9:1	0.3:1	1.6:1
Age* at diagnosis of FA				
mean	10	12	13	9
median	9	9	10	6
range	0.1–28	1–31	0.1–34	1–48
percentage >16 years	20%	21%	30%	11%
Age at complication				
mean	14	16	23	16
median	14	16	26	13
range	0.1–29	2–43	0.3–38	3–48
Number without pancytopenia (%)	21 (25%)	19 (28%)	8 (17%)	1 (3%)
Number without androgens (%)	40 (48%)	40 (63%)	18 (38%)	1 (3%)
Number reported deceased (%)	66 (79%)	36 (53%)	28 (60%)	32 (86%)

Notes:

* Ages are in years. 148 patients had one or more malignancy (myelodysplastic syndrome or MDS was not counted as a malignancy); the number of malignancies was 155. MDS cases include nine who developed leukemia; the others are not included in the total.

Patients with tumors after bone marrow transplantation are not included. Adapted from Alter, 1996.

hemopoietic cells is very small. Bone marrow transplant was also difficult, with <40% survival. This topic will be discussed more extensively in Chapter 19.

The IFAR has attempted to address the risk of leukemia in a prospective manner (Butturini et al., 1994). Unfortunately, their report did not always distinguish leukemia from myelodysplastic syndrome (MDS, see later). They suggested that the cumulative risk of development of MDS/AML was 50% by the age of 35. However, since MDS may not necessarily mean the inevitable development of leukemia in the context of FA (see later), the distinction may be important. They did report a 9% incidence of AML (35 of 388 patients), and one patient with acute lymphoblastic leukemia, data resembling our literature review.

Myelodysplastic syndrome

The definition of MDS is generally based on the French–American–British classification scheme (Bennett et al., 1982), and usually involves pancytopenia with

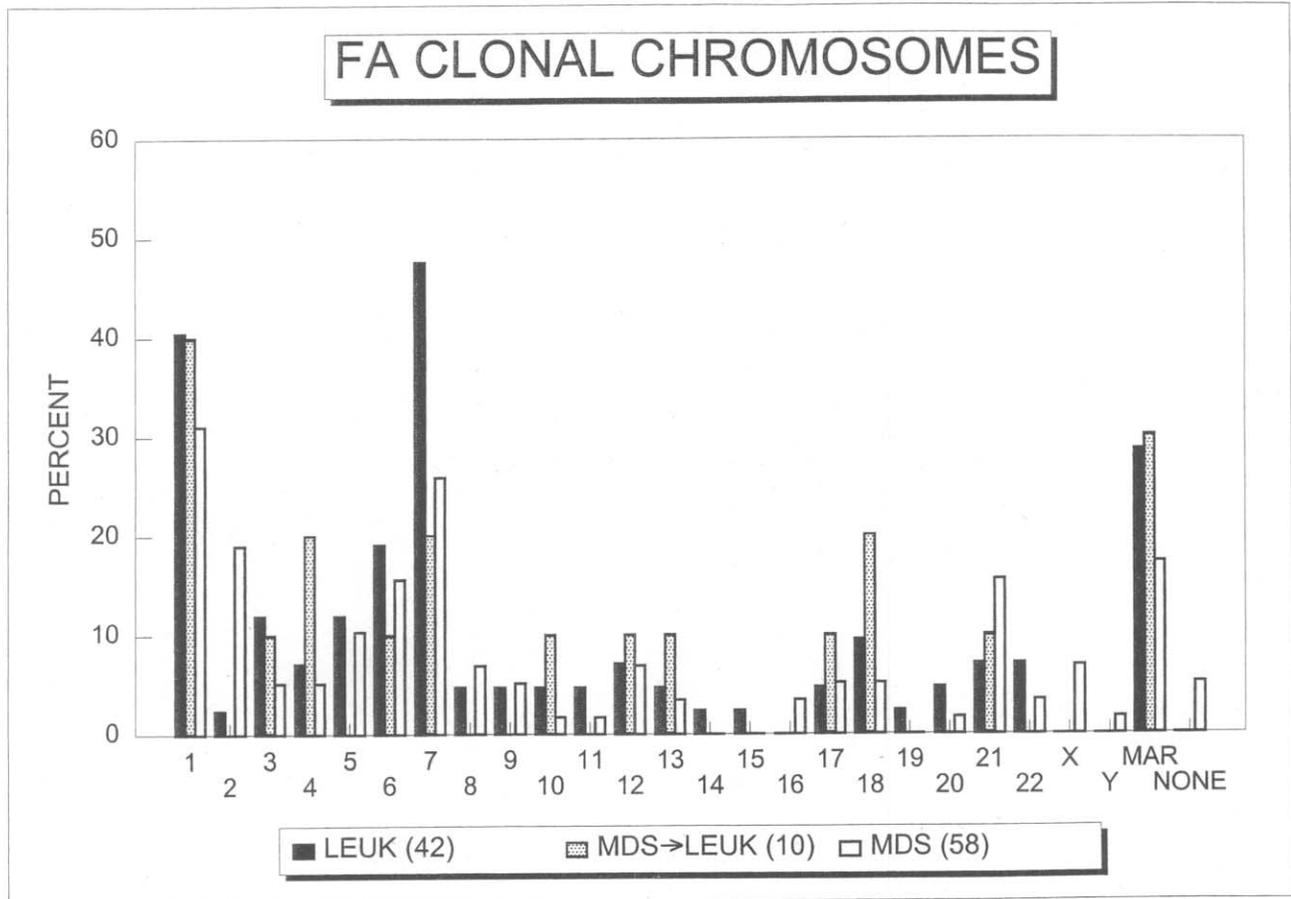


Figure 17.1. Frequency of involvement of specific chromosomes in clonal cytogenetic abnormalities in Fanconi's anemia (FA) patients with leukemia and/or myelodysplastic syndrome (MDS). Black bars, 42 patients with leukemia who had clonal abnormalities. Gray bars, 10 patients who had documented MDS prior to development of leukemia. Open bars, 58 patients who had MDS and had not developed leukemia. MAR, marker chromosome. None indicates that there were no abnormal chromosomes. Data show the proportions of patients in each category with involvement of the designated chromosomes. Many patients had more than one clonal pattern. From Alter, 1996.

very important. In addition to the ten literature cases with a clone on the first study who then developed leukemia, one patient with morphologic MDS developed a clone on a later study, and four with clones developed new independent clones on repeat studies. Among 22 patients with serial studies who did not develop leukemia, 13 had the appearance of new clones. Several patients had marrow examinations in which previously observed clones had disappeared, only to have the same or a different clone reappear later. Thus, detection of a clone may in part be coincidental, since a single patient might be termed 'clonal' or 'nonclonal', depending on the status of the fluctuation.

An International Scoring System was recently proposed in order to classify adult MDS according to cytogenetic findings (Greenberg et al., 1997). A good prognosis consisted of a normal pattern, or one of del(5q), del(20q), or -Y; intermediate was trisomy 8, single miscellaneous, or double abnormalities; while a

poor prognosis was associated with complex anomalies (three or more), or anomalies of chromosome 7. Application of this system to the published FA MDS patient data led to an even division between intermediate and poor cytogenetics, both among those who did develop leukemia and those who did not. It appears that 'MDS' and/or clonal abnormalities in FA patients may not be comparable to adult primary MDS, and require their own interpretation. Hemopoiesis derives from a finite number of stem cells. At different time points, hemopoiesis may be derived from different stem cells. In FA, perhaps related to a defect in DNA repair, the stem cell clones may be identified by cytogenetic abnormalities. Clones may fluctuate, disappearing because of poor growth of mutant cells, or through overgrowth by normal or other mutant clones. Observation of a clone may represent a window in time, but the malignant implication of that clone remains to be demonstrated. The evidence that MDS is a prelude to leukemia is not convincing from the data available so far.

Cancer

Solid tumors are underemphasized in FA, perhaps because they usually occur in relatively older patients, and were not clinically important when patients were not surviving beyond their teens due to fatal AA. However, bone marrow transplant (and perhaps gene therapy) will result in a longer life expectancy. In addition, physicians are more sensitive to the diagnosis of FA, and patients are being diagnosed when older, as well as without characteristic physical anomalies. With all the caveats relative to the bias of literature reports, 55 tumors were reported in 45 patients, representing approximately 5% of the case reports (Alter, 1996). An unexpected observation is that the ratio of females to males was 3:1, even after exclusion of gynecologic malignancies. Most tumors were squamous cell carcinomas and occurred at a mean age of 23 years, which is much younger than when most of the same tumors are seen in the nonFA population. The major sites of the tumors were oropharyngeal, gastrointestinal, and gynecological, and the specific locations are summarized in Table 17.4. Eleven patients had two or more primaries, including two with liver cancer and two with leukemia.

These cancers were diagnosed when the FA patients were in their twenties, generally later than when most FA patients reported in the literature develop AA (mean age of 8 years), leukemia (14 years), liver tumors (16 years) and myelodysplasia (17 years) (Table 17.3). It thus appears that FA patients who do not succumb to AA remain at risk of other malignancies, with solid tumors coming last.

There are reports of at least six FA patients (equally males and females) whose hemopoietic disease was cured by bone marrow transplantation, but who developed solid tumors 2–12 years later (Bradford et al., 1990; Flowers et al., 1992;

Table 17.4. Types of cancer in Fanconi's anemia

Type	Number		
	of tumors	Males	Females
Oropharyngeal	16	5	11
Cricoid	1	—	1
Gingiva	4	2	2
Gingiva, tongue	1	1	—
Jaw, benign	1	—	1
Mandible	1	—	1
Pharynx	1	1	—
Tongue	7	1	6
Gastrointestinal	15	4	11
Anus	3	—	3
Anus Bowen's	1	—	1
Colon, anus	1	—	1
Esophagus	8	2	6
Gastric adenoca	2	2	—
Gynecological	12	—	12
Breast	4	—	4
Cervix	1	—	1
Cervix, vulva	1	—	1
Vulva	6	—	6
Brain	4	1	3
Astrocytoma	2	—	2
Medulloblastoma	2	1	1
Other	9	1	8
Bone marrow lymphoma	1	—	1
Bronchopulmonary	1	1	—
Eyelid Bowen's	1	—	1
Renal	1	—	1
Skin	2	—	2
Bowen's	1	—	1
Wilms'	1	—	1
Retinoblastoma	1	—	1
Total	56	11	45

Notes:

Number of tumors (56) exceeds number of patients (47); 11 had > 2 primaries, including 2 with liver cancer and 2 with leukemia. Modified from Alter, 1996.

Millen et al., 1997; Murayama et al., 1990; Socié et al., 1991; Somers et al., 1994). Bone marrow transplantation preparation included irradiation (three) and cyclophosphamide (200 mg/kg in two, 20 mg/kg in the others), and four of the patients had chronic graft-versus-host disease (GVHD). One patient had independent cheek and tongue cancers 5 years apart, four had tongue cancer, and one had cheek cancer. The relative roles of the immunosuppressive preparation and GVHD are not clear; both may be blamed. In addition, since oropharyngeal cancers were the most common in the nontransplanted FA patients, these tumors may represent the natural history of FA, perhaps accelerated by bone marrow transplantation. The frequency of these tumors may already be as high as 5% of transplanted patients, with more to come.

Liver disease

Approximately 5% of reported FA patients had liver disease, usually a tumor (Alter, 1996). All but one had received androgens. Diagnoses were made at a mean of 16 years of age, and the male:female ratio was 1.6:1 (Table 17.3). The tumors were called 'hepatocellular carcinoma' or 'hepatoma' in 20 patients; two were called 'benign', two had adenomas, and only one had metastases and an increased level of alpha-fetoprotein. Six patients had adenomas, one of which had metastases, and two were unclassified. It is possible that these pathologic distinctions were not entirely clear-cut, but included dysplasia, similar to the apparent myelodysplasia seen in the bone marrows. Five patients also had leukemia, and one each tongue and esophageal cancer. Liver tumors were only found at autopsy following death from other causes in four patients. Six patients had peliosis hepatis with the tumors, while another seven had peliosis alone. Several patients stopped androgen therapy (including having bone marrow transplantation), and the tumors regressed. Eighty-five percent of those with liver tumors died, but not directly from their tumor; they died from the underlying hematological problems.

Reproduction

As discussed above, AA is not the only major problem for patients with FA, a condition which is considered to be premalignant. However, FA patients are living longer than before, and are being diagnosed with milder phenotypes. The complications summarized in Table 17.3 are not the only problems for the older patients.

Older females have nonmalignant gynecological problems, including delayed menarche, irregular menses, and early menopause, which can result in low estrogen levels and osteoporosis. Female fertility is probably reduced, but not absent. Twenty-nine pregnancies were reported in 19 women, with seven

Table 17.5. Median survival age in Fanconi's anemia (FA)

Condition	Age (years)
All FA, 1927–94	19
All FA, 1991–94	30
Cancer	28
Liver disease	13
All leukemia	15
Leukemia with clone	19
MDS → leukemia	19
MDS no leukemia	25
MDS intermediate cytogenetics	21
MDS poor cytogenetics	35

miscarriages, 22 births, and 21 surviving children (Alter and Young, 1998; Alter et al., 1991*a*). Half of the mothers needed red blood cell and/or platelet transfusions during the pregnancies or at delivery. There were six Cesarean sections because of failure of labor to progress, and four cases with preeclampsia or eclampsia. No FA mother died intrapartum, but nine died later at ages 24–45 years, primarily from cancer.

In addition, males are small, with gonads that are underdeveloped, and abnormal spermatogenesis (Bargman et al., 1977). The number of FA males reported to have children is less than half a dozen (Alter and Young, 1998). Infertility is a frequent complaint among the older FA males, particularly for those diagnosed as adults. Indeed, documented infertility caused by azoospermia in a male with 'acquired' AA should lead to consideration of FA.

Prognosis

The survival of all patients with FA has improved with time (Table 17.5), with the median reaching more than 30 years of age recently. This reflects improvements in the management of AA (see Chapter 19), including better supportive care, but also the inclusion of patients whose phenotype is milder than that of the 'classic' patients of the early years. Figure 17.2 and Table 17.5 indicate median survivals for patients with various major complications, including leukemia, cancer, liver disease, and MDS. The older median survival age in patients with cancer, for example, does not necessarily imply that cancer has a good prognosis, but that the subset of patients who developed cancer may have had a milder phenotype, and did not succumb earlier to hematologic

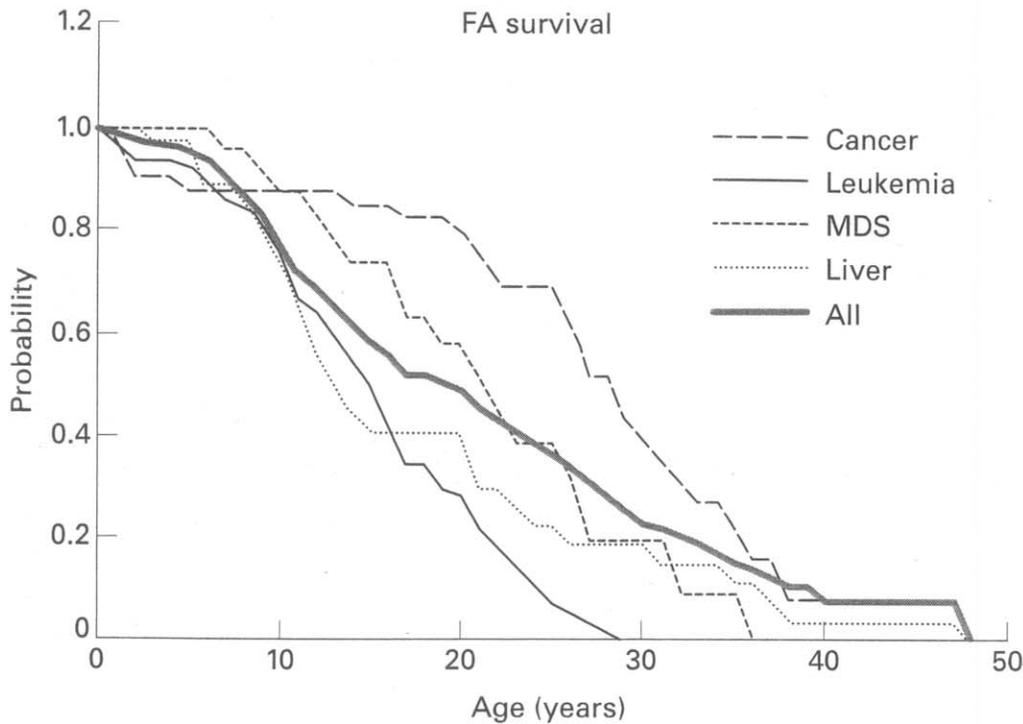


Figure 17.2. Kaplan-Meier survival curves for all FA patients reported in the literature since 1927. The center line shows the curve for all patients. The marked lines are for patients with leukemia (Leuk), MDS, liver disease (mostly tumors), and solid tumors (Ca).

disease. The ability to offer prognoses in FA will improve as the diagnosis becomes more specific at the molecular level.

Conclusion

The diagnosis of FA is easily made in the 'textbook' patient who has AA and characteristic birth defects. This group may represent 75% of cases, but the actual number will remain unclear until all of the genes have been cloned, and all cases of AA at all ages are studied at the molecular level. The most important component of the diagnosis of FA is thinking of it, which leads to testing (currently done with chromosome breakage analysis), which will probably identify more than 90% of cases. The unusual presentations alluded to in this chapter include AA at an older age (i.e., cared for by adult not pediatric hematologists), or AML or solid tumor without antecedent AA, with or without the FA physical phenotype. The diagnosis of FA will be made by those who think of it in the atypical circumstances.

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