Frequency and natural history of inherited bone marrow failure syndromes: the Israeli Inherited Bone Marrow Failure Registry

Hannah Tamary,[1] Daniella Nishri,[2] Joanne Yacobovich,[1] Rama Zilber,[1] Orly Dgany,[3] Tanya Krasnov,[3] Shraga Aviner,[4] Polina Stepensky,[5] Shoshana Ravel-Vilk,[5] Menachem Bitan,[6] Chaim Kaplinsky,[7] Ayelet Ben Barak,[8] Ronit Elhasid,[8] Joseph Kapelusnik,[9] Ariel Koren,[10] Carina Levin,[10] Dina Attias,[11] Ruth Laor,[11] Isaac Yaniv,[1] Philip S. Rosenberg,[12] and Blanche P. Alter[13]

[1]Pediatric Hematology/Oncology Department, [2]Departmant of Pediatrics C, Schneider Children's Medical Center of Israel, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [3]Pediatric Hematology Laboratory, Felsenstein Medical Research Center, Beilinson Campus, Petah Tiqva, Israel; [4]Department of Pediatrics, Barzilai Medical Center, Ashkelon, Israel; [5]Pediatric Hematology/Oncology Unit and [6]Bone Marrow Transplant Unit, Hadassah Medical Center, Jerusalem, Israel; [7]Pediatric Hematology/Oncology Department, Sheba Medical Center, Tel Hashomer, Israel; [8]Pediatric Hematology/Oncology Department, Rambam Medical Center, Haifa, Israel; [9]Pediatric Hematology/Oncology Unit, Soroka Medical Center, Beer Sheba, Israel; [10]Pediatric Hematology Unit, Ha'Emek Medical Center, Afula, Israel; [11]Pediatric Hematology/Oncology, Bnai Zion, Medical Center, Israel; [12]Biostatistics Branch, and [13]Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

ABSTRACT

Background

Inherited bone marrow failure syndromes are rare genetic disorders characterized by bone marrow failure, congenital anomalies, and cancer predisposition. Available single disease registries provide reliable information regarding natural history, efficacy and side effects of treatments, and contribute to the discovery of the causative genes. However, these registries could not shed light on the true incidence of the various syndromes. We, therefore, established an Israeli national registry in order to investigate the relative frequency of each of these syndromes and their complications.

Design and Methods

Patients were registered by their hematologists in all 16 medical centers in Israel. We included patients with Fanconi anemia, severe congenital neutropenia, Diamond-Blackfan anemia, congenital amegakaryocytic thrombocytopenia, dyskeratosis congenita, Shwachman-Diamond syndrome, and thrombocytopenia with absent radii.

Results

One hundred and twenty-seven patients diagnosed between 1966 and 2007 were registered. Fifty-two percent were found to have Fanconi anemia, 17% severe congenital neutropenia, 14% Diamond-Blackfan anemia, 6% congenital amegakaryocytic thrombocytopenia, 5% dyskeratosis congenita, 2% Shwachman-Diamond syndrome, and 2% thrombocytopenia with absent radii. No specific diagnosis was made in only 2 patients. Of the thirty patients (24%) developing severe bone marrow failure, 80% had Fanconi anemia. Seven of 9 patients with leukemia had Fanconi anemia, as did all 6 with solid tumors. Thirty-four patients died from their disease; 25 (74%) had Fanconi anemia and 6 (17%) had severe congenital neutropenia.

Conclusions

This is the first comprehensive population-based study evaluating the incidence and complications of the different inherited bone marrow failure syndromes. By far the most common disease was Fanconi anemia, followed by severe congenital neutropenia and Diamond-Blackfan anemia. Fanconi anemia carried the worst prognosis, with severe bone marrow failure and cancer susceptibility. Diamond-Blackfan anemia had the best prognosis. The data presented provide a rational basis for prevention programs and longitudinal surveillance of the complications of inherited bone marrow failure syndromes.

Key words: inherited bone marrow failure syndromes, Fanconi anemia, stem cell transplantation.

Citation: Tamary H, Nishri D, Yacobovich J, Zilber R, Dgany O, Krasnov T, Aviner S, Stepensky P, Ravel-Vilk S, Bitan M, Kaplinsky C, Ben Barak A, Elhasid R, Kapelusnik J, Koren A, Levin C, Attias D, Laor R, Yaniv I, Rosenberg PS, and Alter BP. Frequency and natural history of inherited bone marrow failure syndromes: the Israeli Inherited Bone Marrow Failure Registry. Haematologica 2010;95(8):1300-1307. doi:10.3324/haematol.2009.018119

©2010 Ferrata Storti Foundation. This is an open-access paper.

Acknowledgments: we thank Prof. I. Dokal for the molecular diagnosis of patients with dyskeratosis congenita.

Funding: this work was supported in part by a grant from the Israel Cancer Association, and by the Intramural Research Program of the National Institutes of Health and the National Cancer Institute of the United States.

Manuscript received on October 6, 2009. Revised version arrived on January 22, 2010. Manuscript accepted on January 28, 2010.

Correspondence:
Hannah Tamary MD,
Pediatric Hematology Oncology,
Schneider Children's Medical Center of Israel, 14 Kaplan Street, Petah Tiqva 49, 202, Israel.
E-mail: htamary@post.tau.ac.il

Introduction

Inherited bone marrow failure syndromes are a group of rare genetic disorders characterized by bone marrow failure, congenital anomalies, and cancer predisposition.[1] The inherited bone marrow failure syndromes include disorders associated with pancytopenia, such as Fanconi anemia and dyskeratosis congenita, as well as disorders with predominantly, but not exclusively, single lineage cytopenias, such as Diamond-Blackfan anemia, severe congenital neutropenia, Shwachman-Diamond syndrome, congenital amegakaryocytic thrombocytopenia, and thrombocytopenia with absent radii.[2-7]

Single disease registries, which have been established worldwide since the 1980s, are dedicated to patients diagnosed with Fanconi anemia, Diamond-Blackfan anemia, or dyskeratosis congenita[5,8-9] The Severe Congenital Neutropenia International Registry differs in that it collects data on all patients with neutropenia treated with granulocyte colony stimulating factor (G-CSF).[10] These registries provide more reliable information than case series regarding clinical presentation, natural history, and response to therapy. Analysis of the data collected in the registries made it possible to evaluate the efficacy and side effects of treatments and contributed to the discovery of the causative genes.[5,8-10] However, these registries, being disease-specific or treatment-specific, cannot shed light on the true incidence of the various syndromes.

We established a retrospective population-based national registry of inherited bone marrow failure syndromes in Israel. Using this registry, we calculated the relative frequency of each of the inherited bone marrow failure syndromes, the birth rate of Fanconi anemia, and the frequency of complications. Using previously described methods, we performed quantitative analysis of the risks of adverse events in Fanconi anemia.[11-13]

Design and Methods

Registry

Patients were registered from all 16 pediatric hematology-oncology centers in Israel. Referral to the registry was made by the treating physician. Recruitment included both living and deceased patients diagnosed between 1966 and 2007. The studies were approved by the research ethics committee of the Rabin Medical Center, as well as by the ethics committees in each of the participating centers. Since this was a chart review study, individualized consent forms were not required.

The data collecting form used is a modification of the one developed by Alter *et al.* and was used for the North American Survey of Fanconi anemia (NAS) and in an expanded version for the ongoing National Cancer Institute inherited bone marrow failure syndromes Study (www.marrowfailure.cancer.gov).[11] Our questionnaire included data regarding: 1) demographics; 2) laboratory tests supporting the diagnosis, including molecular diagnosis; 3) physical examination; 4) hematologic information: complete blood counts (CBC) at diagnosis, at onset of pancytopenia, and at the last follow up; 5) treatment: medical, supportive, and stem cell transplantation (SCT) dates and SCT complications; 6) malignancy, including types of cancer and date/age at onset.

A research nurse (RZ) or a physician (DN) filled out the questionnaire after a review of the patients' charts at each center. The diagnosis of each patient was approved by a senior investigator (HT) based on the best available current diagnostic criteria for each disease. Only questionnaires that included sufficient data were included. Each questionnaire was individually entered into a Microsoft Excel spreadsheet.

Inclusion criteria

Fanconi anemia

Individuals demonstrating an appropriate clinical picture supported by the abnormal chromosomal breakage test[2] and if available by mutation in one of the genes.[14]

Dyskeratosis congenita

Individuals exhibiting the typical clinical features[15] supported, when available, by the presence of a mutation in the *DCK1*, *TERT* or *TERC* genes.[16]

Diamond-Blackfan anemia

Individuals fulfilling the classic diagnostic criteria,[4,17] supported, if available, by increased erythrocyte adenosine deaminase (eADA) activity and/or by mutation in the *RPS19*, *RPS24*, *RPS17*, *RPL5*, *RPL11* or *RPL35A* genes.[18]

Shwachman-Diamond syndrome

Individuals exhibiting neutropenia associated with exocrine pancreatic insufficiency and, if possible, by mutation in the *SBDS* gene.[6]

Severe Congenital Neutropenia

Individuals with an appropriate clinical picture and, if available, by mutations in *ELA2*, *HAX1*, *G6PC3* or *WAS* genes.[19]

Congenital amegakaryocytic thrombocytopenia

Individuals who presented with early-onset thrombocytopenia, typical bone marrow findings, and mutations in the thrombopoietin receptor (*cMPL*) gene.[7]

Thrombocytopenia with absent radii

Individuals with typical clinical manifestations.[7]

Bone marrow failure-not otherwise specified

Individuals who presented with marrow failure and were suspected to have inherited bone marrow failure by the combination of young age at presentation, low birth weight, macrocytosis and high levels of hemoglobin F. However, no specific diagnosis could be made as there was normal chromosomal breakage test, normal telomere length, and no mutations in *SBDS* or c-MPL genes.

Hematologic criteria

As previously suggested, severe bone marrow failure was defined as associated with pancytopenia, necessitating stem cell transplantation or causing death.[12] Diagnosis of myelodysplastic syndrome (MDS) was made by the presence of chromosomal aberration and/or 5-20% blasts in bone marrow. Since MDS does not always develop into leukemia, MDS data were analyzed separately from leukemia.

The Fanconi anemia birth rate and calculations

We estimated the Fanconi anemia birth rate using a direct approach that divided the numbers of cases enrolled in the registry according to birth year by the corresponding numbers of live births in Jews and non-Jews, respectively.[20] The allele frequency was then estimated using the Hardy-Weinberg law.

Statistical Methods

The follow-up period for living patients was calculated by using the date of the last follow up at the treating medical center, minus

the date of diagnosis. If the date of the last follow up was not available, we used the date when the questionnaire was filled out. Deceased patients were censored at the time of death. Descriptive data are presented as percentages, medians, and ranges. Analyses were performed using the Microsoft Excel-XP program.

A competing risks approach to estimate cause-specific hazard functions and cumulative incidence curves for bone marrow failure, acute myeloid leukemia, and solid tumors was performed as previously described.[11-13] For each specific type of cancer the observed number of cancer cases occurring prior to transplant was compared with the expected number (O/E ratio) based on the experience of the United States Surveillance, Epidemiology and End Results Program (SEER 9).[21] For Fanconi anemia, we also studied the association between the risk of severe bone marrow failure and leukemia and the previously identified five-item congenital abnormality scale with possible values ranging from 0 through 5.[13] Survival was described using the Kaplan-Meier method.

Results

Demographics

One hundred and fifty-nine living and deceased patients were registered between August 1st 2005 and January 31st 2008. Sixteen patients (10%) were omitted because there were not enough data to support the proposed diagnosis or to allow statistical analysis (most did not have a complete blood count; 8 were suspected to have Fanconi anemia, 5 severe congenital neutropenia, and 3 Diamond-Blackfan anemia). Another 16 were only known by name; they were mostly family members of included patients for whom no questionnaire was filled out and they were probably lost to follow up. The final review includes 127 patients (80%), of whom 65 were males (51%) and 62 females (49%). The earliest birth year was 1958. Demographic data are presented in Table 1.

At the time of analysis, 89 patients (70%) were alive, 34 (27%) were dead, and 4 additional patients (all Fanconi anemia) were lost to follow up. The youngest living subject was a 3-month old patient with Diamond-Blackfan anemia and the oldest was a 42-year old patient with Fanconi anemia. The median age at diagnosis was 2.2 years (range, birth to 26.5 years). The median follow-up period at the primary medical center before inclusion in the registry was 5.8 years (range, 0-39.1 years). Seventy-two (56%) patients were of Jewish origin and 55 (44%) were of Arabic origin.

Relative frequencies of the different disorders

The relative frequency of each disease is presented in Table 1. Sixty-six (52%) patients were found to have Fanconi anemia, 21 (17%) severe congenital neutropenia, 18 (14%) Diamond-Blackfan anemia, 8 (6%) congenital amegakaryocytic thrombocytopenia, 6 (5%) dyskeratosis congenita, 3 (2%) Shwachman-Diamond syndrome, and 3 (2%) thrombocytopenia with absent radii. It should be noted that 2 patients (one with dyskeratosis congenita and the other with Shwachman-Diamond syndrome) were initially diagnosed as having acquired aplastic anemia. The correct diagnosis was reached, however, two and three years following the initial diagnosis with the appearance of dysplastic nails and exocrine pancreatic insufficiency, respectively. In 2 patients (2%), although an inherited bone marrow failure syndrome was suspected, no specific diagnosis could be made. These patients presented at an early age (one and three years old) to consanguineous families. They were small for gestational age and had macrocytosis as well as high hemoglobin F levels. Normal chromosomal breakage test, normal telomere length, as well as no mutations in *SBDS* or c-MPL genes precluded precise diagnosis. Both are growing well with moderate pancytopenia 5-7 years after diagnosis.

Consanguinity and molecular diagnosis

Ninety-eight families were included in the registry. Consanguinity was recorded in 50 patients (40%; Table 1). Fifty-six patients (44%) had other affected family members; most of them were included in the registry. Eighty-six patients (68%) underwent molecular genetic testing and pathogenic mutations were identified in 62 patients (72% of those examined) (Table 2).

Birth rates

The birth rate was calculated for the most common disease, Fanconi anemia. The direct estimate was obtained from the registry based on Fanconi anemia cases registered during the 1980s. This period was chosen because cases born in earlier years might have been missed,

Table 1. Demographic data of patients in the Israeli Inherited Bone Marrow Failure Registry (IS-IBMFR, n=127).

N. of patients	FA	SCN	DBA	CAMT	DC	SDS	TAR	NOS*	All
Total (%)	66 (52)	21 (17)	18 (14)	8 (6)	6 (5)	3 (2)	3 (2)	2 (2)	127 (100)
N. of families	46	17	18	6	4	3	2	2	98
Male: Female	33:33	11:10	8:10	3:5	5:1	2:1	1:2	2:0	65:62
Jewish: Arab	36:30	9:12	13:5	1:7	6:0	3:0	3:0	1:1	72:55
Consanguinity (%)	34 (68)	8 (16)	2 (4)	3 (6)	1 (2)	--	--	2 (4)	50 (40)
Age at diagnosis, yrs, median (range)	6.25 (0-26.5)‡	0.08 (0-0.65)‡	0.2 (0-2.4)	0.6 (0-1)	8.9 (1-20.8)	1 (0-2.4)	0	0.8 (0.6-1)	2.2 (0-26.5)§
Age at follow up, yrs, median (range)	6.2 (0-39.1)‡	6.8 (0.8-32)‡	7.3 (0.25-27.25)	4.3 (2.25-11.8)	5.4 (0.2-11.8)	4.25 (1.6-9.7)	3 (0.2-3.2)	2.7 (1.5-3.9)	5.8 (0-39.1)§
Person-years	547‡	170.5‡	132.3	42.2	36.3	15.5	6.3	6.25	956.2

*FA: Fanconi anemia; DC-dyskeratosis congenita; DBA-Diamond-Blackfan anemia; SCN-severe congenital neutropenia; SDS-Shwachman-Diamond syndrome; CAMT-congenital amegakaryocytic thrombocytopenia; TAR-thrombocytopenia with absent radii; *NOS-not otherwise specified; in brackets % of total number with an IBMFS; Person-years: the total sum of the number of years from diagnosis; ‡Data on one patient are missing; §Data on 2 patients are missing.*

Table 2. Israeli Inherited Bone Marrow Failure Registry Genetic Analysis (n=62)

N. of patients	Disease	Affected gene	Mutation 1	Mutation 2	Effect 1	Effect 2	Ethnicity
2	FA	*FANCA*	c.3785_3787del3	c.3785_3787del3	Absence of AA	Absence of AA	Arab
7		*FANCA*	c.2172_2173insG	c.2172_2173insG	Frame shift	Frame shift	Moroccan Jewish
1		*FANCA*	c.2172_2173insG	c.4275delT	Frame shift	Frame shift	Moroccan Jewish
1		*FANCA*	c.2172_2173insG	c.890_893del	Frame shift	Altered splicing	Moroccan / Tunisian Jewish
2		*FANCA*	Del exon 31-37	c.4275delT	Nonsense	Frame shift	Yemenite /Moroccan Jewish
4		*FANCA*	c.2574C>G	c.2574C>G	p.Ser858Arg	p.Ser858Arg	Indian Jewish
4		*FANCA*	c.523_3066del	c.523_3066del	Nonsense	Nonsense	Arab
4		*FANCA*	c.4168-2A>C	c.4168-2A>C	Altered splicing	Altered splicing	Arab
1		*FANCA*	c.3382C>T	c.3382C>T	Gln1128Ter	Gln1128Ter	Arab
5		*FANCC*	c.425+4A>T	c.425+4A>T	Altered splicing	Altered splicing	Ashkenazi
1		*FANCC*	c.425+4A>T	Not Found	Altered splicing		Mixed Jewish
1		*FANCC*	c.425+4A>T	Not Found	Altered splicing		Mixed Jewish
1		*FANCD1*	c.6174delT	Not Found	Frame shift		Mixed Jewish
2		*FANCG*	c.509+3A>G	c.509+3A>G	Altered splicing	Altered splicing	Arab
1		*FANCG*	c.212T>C	c.212T>C	p.Leu71Pro	p.Leu71Pro	Arab
3		NI					Arab (3)
26		ND					Ashkenazi (4), Sephardic (9), Arab (12)
2	SCN	*ELA2*	c.468G>C		p.Trp156Cys		Arab
2			c.709C>T		p.Gln237Ter		Sephardic
1			c.597+5G>A		Altered splicing		Arab
1			c.597+5G>A		Altered splicing		Mixed Jewish
1			c.597+1G>T		Altered splicing		Sephardic
9		NI					Arab (7), Sephardic (2)
5		ND					Arab (2), Mixed Jewish (2), Sephardic (1)
1	DBA	*RPS19*	c.173_177del		Altered splicing		Sephardic
1		*RPS19*	c.356-22del18		Altered splicing		Mixed Jewish
1		*RPS19*	c.185G>A		p.Arg62Gln		Ashkenazi
1		*RPS19*	c.443+1G>A		Altered splicing		Ashkenazi
3		NI					Sephardic (2), Mixed (1)
11		ND					Ashkenazi (2), Sephardic (3), Mixed (2), Arab (4)
1	CAMT	*cMPL*	c.76C>T	c.76C>T	Gln26Ter	Gln26Ter	Bedouin
1		*cMPL*	c.127C>T	c.127C>T	Arg43Ter	Arg43Ter	Arab
3		*cMPL*	c.212+5 G>A	c.212+5 G>A	Altered splicing	Altered splicing	Arab
1		*cMPL*	c.460T>C	c.460T>C	Trp154Arg	Trp154Arg	Druze
1		*cMPL*	c.1162G>T	c.1162G>T	Ala388Ser	Ala388Ser	Unknown
1		*cMPL*	c.1031T>A	c.1031T>A	Leu344Gln	Leu344Gln	Mixed Jewish
1	DC	*DKC1*	c.1050C>T		p.Ala353Val		Sephardic
2		*TERT*	c.1892G>A		p.Arg631Gln		Sephardic (Iraq)
1		*TERT*	c.2701C>T	c.2701C>T	p.Arg901Trp	p.Arg901Trp	Sephardic (Iran)
1		NI					Mixed
1		ND					Sephardic
1	SDS	*SBDS*	c.183-184 TA>CT	c.258+2T>C	In frame stop-codon	Altered splicing	Mixed
1		NI					Mixed
1		ND					Mixed

FA: Fanconi anemia; DC: dyskeratosis congenita; DBA: Diamond-Blackfan anemia; SCN: severe congenital neutropenia; SDS: Shwachman-Diamond syndrome; CAMT: congenital amegakaryocytic thrombocytopenia; Mixed Jewish Ashkenazi Sephardic Jewish descent; AA: amino acid; Pts: patients; ND: not done because no material available; NI: mutation not identified.

whereas some cases born since 2000 still might not have been diagnosed. For the 1980s, a direct estimate of the birth rate was 2.22 per 100,000 live births, with a 95% confidence interval of 1.5 to 3.4 per 100,000 based on the Poisson distribution. The corresponding estimate of the allele frequency is 1 in 212 (95%CI:1 in 171 to 1 in 258) and the carrier frequency (2pq) is 1 in 107 (95%CI:1 in 86 to 1 in 130). These values are significantly higher than the estimated worldwide birth rate of 0.28 per 100,000 based on the estimated worldwide carrier frequency estimate of 1 in 300.[22]

Overall adverse events

Adverse events evaluated included severe bone marrow failure, malignancy, and mortality. Details of complications are presented in Table 3.

Severe bone marrow failure

Thirty patients (24%) developed severe bone marrow failure as defined by Rosenberg *et al.*[12] at a median age of eight years (range 0.5-30 years; Table 3). The majority of these patients (26 of the 30; 87%) had Fanconi anemia, 3 had congenital amegakaryocytic thrombocytopenia and one had dyskeratosis congenita. The cumulative incidence of bone marrow failure in Fanconi anemia to age 32 was 70% (Figure 1A). The cause-specific hazard of bone marrow failure in Fanconi anemia patients peaked at 10.5% per year at age ten years (95% CI: 6.7-14.1% per year) (Figure 1B). As previously found for Fanconi anemia[12], abnormal radii and a five-item congenital abnormality score (CABS) were together significantly associated with the risk of bone marrow failure (P=0.009); the relative hazard for bone marrow failure increased by 1.6 for every 1-unit increase in the CABS score (95% CI: 1.1-2.2) (*data not shown*).

Malignancy

Fifteen patients (12%) were diagnosed with malignancy: 9 with leukemia and 6 with solid tumors (Table 3). The majority of patients developing malignancy had Fanconi anemia (13 of 15), one had severe congenital neutropenia, and one had congenital amegakaryocytic thrombocytopenia. For Fanconi anemia, the observed/expected (O/E) ratio for cancer was 71 for all cancers, similar to results from other Fanconi anemia registries.[11,13] The cumulative incidence by age of development of cancer in Fanconi anemia, severe congenital neutropenia, and congenital amegakaryocytic thrombocytopenia is shown in Figure 2. The probability of developing cancer by the age of 25 was 30% in Fanconi anemia, 18% for severe congenital neutropenia (Figure 2) and 10% for congenital amegakaryocytic thrombocytopenia. No malignancy was recorded in Diamond-Blackfan anemia, dyskeratosis congenita, Shwachman-Diamond syndrome, or thrombocytopenia

Table 3. Adverse events affecting patients in the Israeli Inherited Bone Marrow Failure Registry (IS-IBMFR, n=127)

N. of patients and ages	FA	SCN	DBA	CAMT	DC	SDS	TAR	NOS*	ALL
Total (%)	66 (52)	21 (17)	18 (14)	8 (6)	6 (5)	3 (2)	3 (2)	2 (2)	127 (100)
Deceased	25 (38)	6 (29)	--	--	2 (33)	1 (33)	--	--	34 (27)
Age at death, yrs, median (range)	11 (3.3-35.8)	3.8 (0.25-18.2)	--	--	16.7 (5.2-28.1)	6.7	--	--	10.6 (0.25-36)
Severe BMF	26 (39)	--	--	3 (38)	1 (17)	--	--	--	30 (24)
Age at severe BMF, yrs, median (range)	10 (4-30)*	--	--	3 (0.5-3)	2		--	--	8 (0.5-30)*
SCT	30 (45)	6 (29)	1 (6)	5 (63)	1 (17)	--	--	--	43 (34)
Age at transplant, yrs, median (range)	9.5 (0.4-30.8)	10.5 (0.2-30.5)	3.1	2.7 (0.6-3.25)	1.9	--	--	--	8.7 (0.2-30.8)
All malignancies (% of all)	13 (19.7)†	1 (4.8)	--	1 (12.5)	--	--	--	--	15 (11.8)
Leukemia (% of all)	7 (11)	1 (4)	--	1 (12.5)	--	--	--	--	9 (7)
Age at leukemia, yrs, median (range)	10 (0.1-20)	31		0.3					8 (0.1-31)
MDS (% of all)	11 (16)	3 (14)	--	1 (12.5)	--	--	--	--	15 (11.8)
Age at MDS, yrs, median (range)	16 (0.5-29.5)	6 (6-13)		2.5					9 (0.5-29.5)
Solid tumors	6 (9)	--	--	--	--	--	--	--	6 (5)
Age at solid tumor, yrs, median (range)	30.7 (29.7-32)‡	--	--	--	--	--	--	--	30.7 (29.7-32)‡

*FA: Fanconi anemia; DC: dyskeratosis congenita; DBA: Diamond-Blackfan anemia ; SCN: severe congenital neutropenia; SDS: Shwachman-Diamond syndrome; CAMT: congenital amegakaryocytic thrombocytopenia; TAR: thrombocytopenia with absent radii; *NOS: not otherwise specified; severe BMF-severe bone marrow failure as defined by Rosenberg et al.[12]; SCT: stem cell transplantation; yrs: years; ALL: acute lymphoblastic leukemia; AML: acute myeloblastic leukemia; MDS: myelodysplastic syndrome; in brackets the percentage of total number with an IBMFS; * Data on 1 patient are missing; †2 patients had both MDS and a solid tumor; ‡Data on 2 patients are missing.*

with absent radii.

Of the 9 leukemia patients, 7 had acute myeloid leukemia (AML) (6 Fanconi anemia, one severe congenital neutropenia), and 2 acute lymphoblastic leukemia (ALL) (one Fanconi anemia, one congenital amegakaryocytic thrombocytopenia). For Fanconi anemia, the median age at diagnosis of leukemia was ten years (range, 6 weeks-20 years). The cumulative incidence in Fanconi anemia of leukemia by age 30 was 13%. The hazard of leukemia was stable at 0.9% per year (95% CI: 0.42-1.85% per year). The CABS was also found to be significantly associated with the risk of developing acute leukemia (P=0.05) in Fanconi anemia and every 1-unit increase in the CABS increased the relative hazard for leukemia by 2.1 (95% CI: 1.0-4.2) (*data not shown*).

All 6 patients who developed solid tumors had Fanconi anemia. The cumulative incidence to age 32 was 17% for solid tumors. The median age at diagnosis of a solid tumor was 30.7 years (range, 29.7-32 years). Most of the solid tumors were squamous cell carcinoma of the head and neck, esophagus, cervix, and vulva. In only one patient did the malignant disease develop following stem cell transplantation. Significantly elevated O/E ratios for cancers were identified for head and neck squamous cell carcinoma (986-fold), tumors of larynx (13,238-fold), vulva (3,701-fold), cervix (244-fold), and breast (88-fold).

For severe congenital neutropenia, the estimated cumulative incidence of acute myeloid leukemia was high; 34% at age 30.

Fifteen (11.8%) patients had myelodysplastic syndromes (11 Fanconi anemia, 3 severe congenital neutropenia, one congenital amegakaryocytic thrombocytopenia) at the median age of nine years (0.5-29.5). The hazard rate for MDS in Fanconi anemia was stable at 1.4% per year (95% CI: 0.76 -2.49% per year) (Figure 1B). The O/E ratio for MDS in Fanconi anemia was over 11,000-fold.

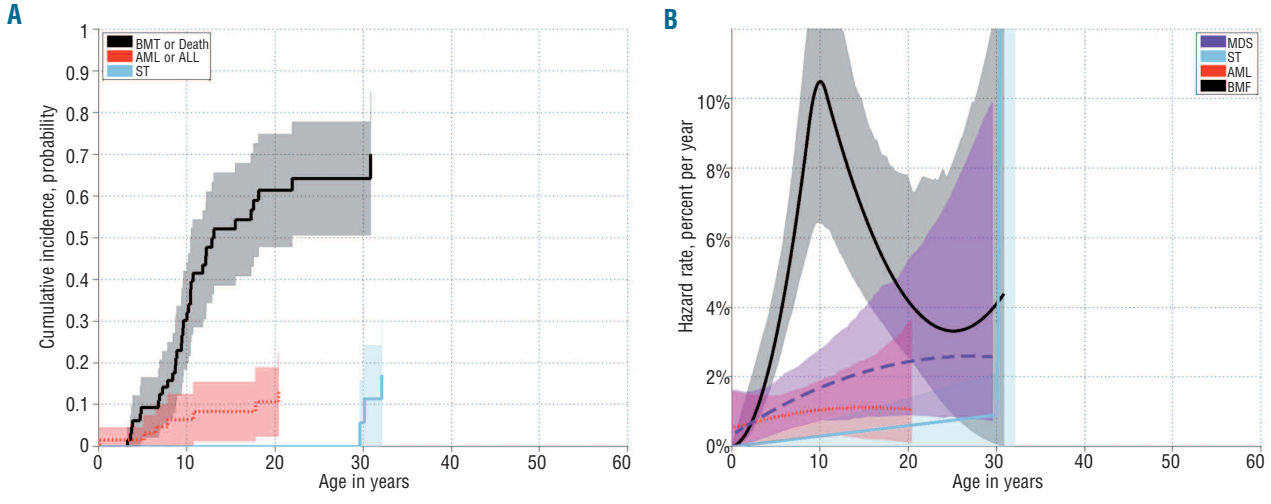

Figure 1. Cumulative incidence by age of adverse events and adverse event rates in IS-IBMFR with Fanconi anemia. (A) Cumulative incidence of the first adverse event, severe bone marrow failure as defined by Rosenberg *et al.*[12], leukemia, and solid tumor (ST), using a competing risk analysis. (B) Annual cause-specific hazard rates of severe BMF, leukemia, myelodysplastic syndrome (MDS), and ST. The shaded areas represent the 95% point-wise confidence intervals.

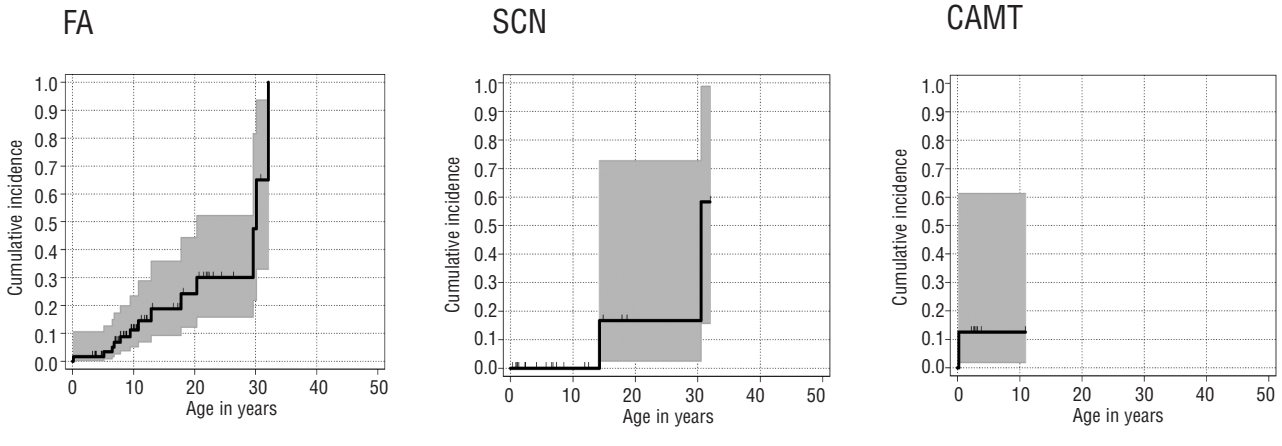

Figure 2. Cumulative incidence by age of development of cancer in IS-IBMFR patients. FA: Fanconi anemia; SCN: severe congenital neutropenia; CAMT: congenital amegakaryocytic thrombocytopenia. The shaded areas represent the 95% point-wise confidence intervals.

Mortality

Thirty-four patients (27%) died from their disease before inclusion in the registry (Table 3). The median age at the time of death was 10.6 years (range, 0.25-35.8 years). Mortality was due to: 1) direct complication of the disease in 5 patients (one Shwachman-Diamond syndrome, 2 dyskeratosis congenita, 2 severe congenital neutropenia); 2) complications of treatment in 12 patients: 11 patients succumbed to complications of stem cell transplantation (8 Fanconi anemia, 3 severe congenital neutropenia), and one Fanconi anemia patient died of hepatic peliosis secondary to long-standing androgen treatment; 3) 15 patients died of either hematologic or solid malignancy, primary or as a consequence of treatment (14 Fanconi anemia, one severe congenital neutropenia). The Kaplan-Meier survival curves for Fanconi anemia, severe congenital neutropenia, Diamond-Blackfan anemia, and congenital amegakaryocytic thrombocytopenia are shown in Figure 3. Survival of patients with Fanconi anemia was 35% at the age of 30 and of patients with severe congenital neutropenia 45% at the age of 20.

Discussion

Accurate epidemiological data regarding inherited bone marrow failure syndromes have been difficult to obtain and are often incomplete. The frequencies of the specific inherited bone marrow failure syndrome categories were estimated mainly from case series.[4-8,10] Our Israeli Inherited Bone Marrow Failure Syndromes Registry is the first population-based national study focused on the inherited bone marrow failure syndromes, including all the major rare syndromes, and it is supported in 47% of cases by molecular testing. This report is based on 127 patients with inherited bone marrow failure syndromes diagnosed in Israel between 1966 and 2007. Studying their records enabled us to determine the relative frequency of each of these disorders, to calculate the Fanconi anemia birth rate, and to evaluate the relative frequency of complications.

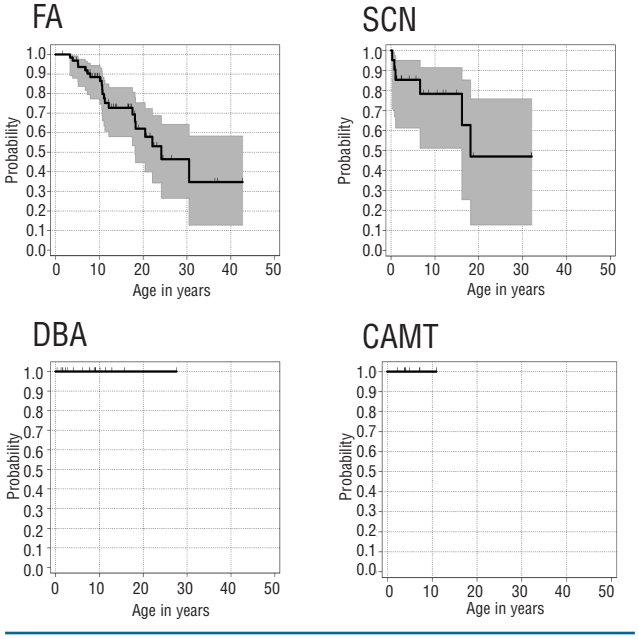

Figure 3. Cumulative survival of IS-IBMFR patients calculated using the Kaplan-Meier method. FA: Fanconi anemia (n=66); SCN: severe congenital neutropenia (n=21); DBA: Diamond-Blackfan anemia (n=18); CAMT: congenital amegakaryocytic thrombocytopenia (n=8). The shaded areas represent the 95% point-wise confidence intervals.

By far the most common inherited bone marrow failure syndrome was Fanconi anemia with 66 patients (52%), followed by severe congenital neutropenia (17%) and Diamond-Blackfan anemia (14%). Congenital amegakaryocytic thrombocytopenia and dyskeratosis congenita were much less common (6% and 5% of patients, respectively) whereas Shwachman-Diamond syndrome and thrombocytopenia with absent radii were each found in 2% of patients (Table 1). Only in 2 of our patients (2%) with an apparent inherited bone marrow failure syndrome were we unable to make a specific diagnosis. The long follow up for some of our patients and the use of molecular diagnosis may have contributed to the low number of patients in our registry for whom a specific diagnosis of inherited bone marrow failure could not be made.

The relatively high proportion of Fanconi anemia patients in our cohort is partly caused by the high rate of consanguinity (52% of Fanconi anemia patients; Table 1) since Fanconi anemia is primarily an autosomal recessive disorder. Indeed, direct population-based calculation of the Fanconi anemia birth rate, made for the first time, yielded a figure of 2.2:100,000 live births (95% confidence interval of 1.5 to 3.4 per 100,000) which is 7-fold higher than expected from the world-wide carrier frequency of 1:300.[22] The majority of our Fanconi anemia patients were either of Sephardic-Jewish extract (38%) or Israeli-Arabs (45%) and, indeed, consanguinity was present in both communities (Table 1). Although the carrier frequency in Ashkenazi Jews is 1 in 90, this group was a minority in our Fanconi anemia families.

The most common disease in our cohort, Fanconi anemia, was also associated with the highest rate of complications and carried the worst prognosis. Severe bone marrow failure as previously defined by Rosenberg *et al.*[12] developed in 30 patients with inherited bone marrow failure syndromes, 26 of whom (87%) had Fanconi anemia. As has been documented previously, Fanconi anemia is a cancer-prone disease.[11] Cancer developed in 15 of our patients, 13 of whom (87%) had Fanconi anemia. Seven of the 9 patients (78%) who developed leukemia and all patients with solid tumors (n=6) had Fanconi anemia. The cumulative incidence (Kaplan-Meier method) of cancer in Fanconi anemia was 30% by the age of 30 (Figure 2) and unstable thereafter due to small numbers. The median survival rate was 35% by the same age (Figure 3).

Despite the relatively small number of Fanconi anemia patients in our registry, compared with two independent and larger Fanconi anemia cohorts from other parts of the world, including the NAS and the German Fanconi Anemia Registry (GEFA),[11,13] complications were qualitatively and quantitatively similar in all three studies. The cause-specific hazards of bone marrow failure, acute myeloid leukemia, and solid tumors (Figure 1), the specific tumors occurring in excess, and the ratios of O/E numbers of cancers were comparable. Additionally, as previously described in the NAS and the GEFA,[12-13] a high five-item congenital abnormality score was associated with an increased bone marrow failure rate and cancer risk. The similarity between our results and those from the NAS and the GEFA supports the validity of our data.

Severe congenital neutropenia was also associated with a low actuarial median survival rate (45% at the age of 20; Figure 3). In contrast, Diamond-Blackfan anemia seemed to have a relatively better prognosis, since none of the patients in our cohort developed any major complications. For patients with dyskeratosis congenita, Shwachman-Diamond syndrome, congenital amegakaryocytic thrombocytopenia, and thrombocytopenia with absent radii, the number of patients is too small to draw any conclusions regarding their relative severity. Dyskeratosis congenita has also recently been documented as a cancer-prone disease,[23] and the absence of such complications in our cohort is probably due to the small number of patients.

This is the first national inherited bone marrow failure syndrome registry capturing the majority of such patients in the country, having a low number of undiagnosed patients (2%), and a relatively long follow-up period (median 5.8, ranging up to 39 years). However, this study has several limitations. The registry originated in a small country and, therefore, included small numbers of patients. A high consanguinity rate may have led to an overrepresentation of autosomal recessive diseases. There was also referral bias, since the data were obtained from pediatric hematology units. We may thus have underestimated patients treated primarily by an adult hematologist, and those who first presented with myelodysplastic syndromes, acute myeloid leukemia, or a solid tumor. This underestimation may also be due to under-diagnosis of patients who were never seen at the collaborating centers or for whom data were incomplete, as well as patients who did not meet diagnostic criteria for any of the known syndromes.

In summary, our data suggest that Fanconi anemia is the most common form of inherited bone marrow failure syndrome in Israel, followed by severe congenital neutropenia and Diamond-Blackfan anemia. The Fanconi anemia population-based calculated birth rate was higher than expected, probably due to consanguinity. Fanconi anemia was associated with the worst prognosis, with a high percentage of patients developing severe bone marrow failure and cancer. Diamond-Blackfan anemia patients had the best prognosis. The data presented provide a rational basis for prevention programs, as well as longitudinal surveillance of the complications of inherited bone marrow failure syndromes.

Appendix

Additional physicians who helped recruit patients: *Sheba Medical Center: D Waldman, A Avidgor, and M Koren, Soroka Medical Center: I Levi, Sha'arei Tzedek Medical Center: H Miskin, Kaplan Medical Center: D Shtager, Soraski Medical Center: R Dvir, Meir Medical Center: B Wollach Carmel Medical Center: E Shved, Western Galilee Medical Center: A Kuperman, Assaf Harofe Medical Center: I Quentzel, Edith Wolfson Medical Center: A Lotan.*

Authorship and Disclosures

HT was the principal investigator and takes primary responsibility for this paper; HT, JI, SA, PS, SV, MB, CK, ABB, JK, AK, CL, and IY recruited patients; DN and RZ reviewed most patients' charts and filled out questionnaires; DN transferred files to the database and participated in statistical analysis; DN and HT wrote the paper; BPA provided the basic protocol and survey instruments for adaptation, helped to analyze data and write the report; PSR helped to analyze data and write the report.

The authors reported no potential conflict of interest.

References

1. Bagby GC. Constitutional marrow failure: Introduction. Semin Hematol. 2006;43(3): 145-6.
2. Bagby GC, Alter BP. Fanconi anemia. Semin Hematol. 2006;43(3):147-56.
3. Skokowa J, Germeshausen M, Zeidler C, Welte K. Severe congenital neutropenia: inheritance and pathophysiology. Curr Opin Hematol. 2007;14(1):22-8.
4. Lipton JM. Diamond blackfan anemia: New paradigms for a "not so pure" inherited red cell aplasia. Semin Hematol. 2006; 43(3):167-77.
5. Vulliamy T, Dokal I. Dyskeratosis congenita. Semin Hematol. 2006;43(3):157-66.
6. Shimamura A. Shwachman-Diamond syndrome. Semin Hematol. 2006;43(3):178-88.
7. Geddis AE. Inherited thrombocytopenia: Congenital amegakaryocytic thrombocytopenia and thrombocytopenia with absent radii. Semin Hematol. 2006;43(3): 196-203.
8. Kutler DI, Singh B, Satagopan J, Batish SD, Berwick M, Giampietro PF, et al. A 20-year perspective on the International Fanconi Anemia Registry (IFAR). Blood. 2003;101 (4):1249-56.
9. Lipton JM, Atsidaftos E, Zyskind I, Vlachos A. Improving clinical care and elucidating the pathophysiology of Diamond Blackfan anemia: an update from the Diamond Blackfan Anemia Registry. Pediatr Blood Cancer. 2006;46(5):558-64.
10. Dale DC, Bolyard AA, Schwinzer BG, Pracht G, Bonilla MA, Boxer L, et al. The Severe Chronic Neutropenia International Registry: 10-Year Follow-up Report. Support Cancer Ther. 2006;3(4):220-31.
11. Rosenberg PS, Greene MH, Alter BP. Cancer incidence in persons with Fanconi anemia. Blood. 2003;101(3):822-6.
12. Rosenberg PS, Huang Y, Alter BP. Individualized risks of first adverse events in patients with Fanconi anemia. Blood. 2004;104(2):350-5.
13. Rosenberg PS, Alter BP, Ebell W. Cancer risks in Fanconi anemia: findings from the German Fanconi Anemia Registry. Haematologica. 2008;93(4):511-7.
14. de Winter JP, Joenje H. The genetic and molecular basis of Fanconi anemia. Mutat Res. 2009;668(1-2):11-9.
15. Dokal I. Dyskeratosis congenita in all its forms. Br J Haematol. 2000;110(4):768-79.
16. Savage SA, Alter BP. Dyskeratosis congenita. Hematol Oncol Clin North Am. 2009; 23(2):215-31.
17. Vlachos A, Ball S, Dahl N, Alter BP, Sheth S, Ramenghi U, et al. Diagnosing and treating Diamond Blackfan anaemia: results of an international clinical consensus conference. Br J Haematol. 2008;142(6):859-76.
18. Lipton JM, Ellis SR. Diamond-Blackfan anemia: diagnosis, treatment, and molecular pathogenesis. Hematol Oncol Clin North Am. 2009;23(2):261-82.
19. Welte K, Zeidler C. Severe congenital neutropenia. Hematol Oncol Clin North Am. 2009;23(2):307-20.
20. Statistics ICBo. Israeli Central Bureau of Statistics. Available from: http://www.cbs.gov.il/energy/shnatonhnew_site.htm.
21. Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, et al. SEER Cancer Statistics Review, 1975-2005. 2008; Available from: http://seer.cancer.gov/csr/1975_2005/.
22. Joenje H, Patel KJ. The emerging genetic and molecular basis of Fanconi anaemia. Nat Rev Genet. 2001;2(6):446-57.
23. Alter BP, Giri N, Savage SA, Rosenberg PS. Cancer in dyskeratosis congenita. Blood. 2009;113(26):6549-57.