Epidemiology of aplastic anemia: a prospective multicenter study

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ABSTRACT

Background

Aplastic anemia is a rare and severe disease. Its incidence varies considerably worldwide. We aimed at describing the epidemiology of this disease, including the incidence, mortality and survival trends, in a well-defined population.

Design and Methods

Since 1980, a case-control surveillance study of aplastic anemia has been carried out by a cooperative group, in the metropolitan area of Barcelona. Inclusion is dependent on the patient having at least two of the following features: white blood cell count $\leq 3.5\times10^9$/L, platelet count $\leq 50\times10^9$/L, hemoglobin <10 g/L or hematocrit of <30%; when only one of these last two criteria is fulfilled, a reticulocyte count of $\leq 30\times10^9$/L is also required. The bone marrow biopsy has to be compatible with the diagnosis of aplastic anemia.

Results

Between 1980 and 2003, a total of 235 cases of aplastic anemia were identified. The overall incidence was 2.34 per million inhabitants per year and the incidence increased with age. Most of the cases were classified as severe or very severe aplastic anemia. Survival rates at 3 months, and at 2 and 15 years after the diagnosis were 73%, 57%, and 51%, respectively. Advanced age and more severe disese at the time of diagnosis were associated with a lower survival rate. There was a trend to a better 2-year survival rate among patients treated with bone marrow transplantation. Forty-nine cases (20.8%) were exposed to drugs reported to be associated with aplastic anemia, and 21 (8.9%) to toxic agents.

Conclusions

The incidence of aplastic anemia in Barcelona is low but the case fatality rate is high. Advanced age and severe disease at the time of diagnosis were associated with decreased survival.

Key words: aplastic anemia, survival, incidence, mortality, risk factors.

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Introduction

Acquired aplastic anemia is an uncommon bone marrow disorder. Laboratory and clinical observations have suggested an immunological etiopathogenesis. Both environmental and individual host factors have been hypothesized to determine risk, although most often aplastic anemia is considered as idiopathic. The disorder has been associated with exposure to chemical agents (benzene, pesticides) and drugs.[1-3] It can also follow viral infections, as post-seronegative hepatitis, and it is a rare complication of pregnancy and other immunological diseases.[2,4]

The incidence of this disease has been found to be low in prospective studies from the United Kingdom,[5] France,[6] Brazil,[7] and in the International Agranulocytosis and Aplastic Anemia Study (IAAAS) conducted in several European countries as well as in Israel.[8] However, higher incidences were usually reported in older studies.[9-11] In addition, the incidence of aplastic anemia shows geographical variability. It seems to be lower in Europe, North America and Brazil, and higher in Asia. Based on the two epidemiological studies carried out in Europe and Asia that used the same methodology, the incidence of the disease is 2-to 3-fold higher in Asia than in the West.[12] This variability in incidence rates may reflect differences in exposure to environmental factors including viruses, drugs and chemicals, genetic background, diagnostic criteria, and study designs.

The case fatality rate of severe aplastic anemia is high although treatment, whether by allogeneic stem-cell transplantation or immunosuppression, has dramatically improved the prognosis over the last 25 years, and more than 75% of patients can now be expected to have long-term survival with either therapy. The outcome of patients with severe aplastic anemia is influenced by patients' variables such as severity of the disease and age, but also by the choice of the initial treatment.[13] We present the results of a 24-year population-based follow-up of patients with aplastic anemia, focusing on trends in incidence, case fatality, mortality and survival.

Design and Methods

From 1980 to 1986, the IAAAS, an international multicenter case-control study, was carried out to assess the risk of blood dyscrasias (agranulocytosis and aplastic anemia) associated with the use of medicines and other risk factors.[8] Although the IAAAS ended in 1986, the surveillance scheme for both dyscrasias continued in Barcelona. The present data refer to aplastic anemia during the period July 1980 to December 2003.

Selection criteria

In order to detect all new patients over the age of 2 years old with aplastic anemia in the study region, our center maintained regular contact with 18 hospitals in the metropolitan area of Barcelona (covering a population of 4.2 to 4.6 million inhabitants) through a designated contact person. Potential cases were patients with at least two of the following criteria: white blood cell count $\leq 3.5\times10^9$/L, platelets $\leq 50\times10^9$/L, hemoglobin <10 g/L or hematocrit of <30%; when only one of the latter two was fulfilled, a reticulocyte count of $\leq 30\times10^9$/L was also required. The bone marrow biopsy had to be compatible with the diagnosis. It also had to be established that the condition was not due to neoplastic or granulomatous disease involving the bone marrow, systemic lupus erythematosus, AIDS, hypersplenism or other conditions associated with pancytopenia such as myelodysplastic syndrome, Fanconi's anemia, and paroxysmal nocturnal hemoglobinuria. Patients exposed to antineoplastic chemotherapy or radiotherapy were excluded. Between 1980 and 1986 cases were blindly reviewed by an IAAAS international committee. Subsequently a hematologist confirmed the diagnosis, by blindly examining the clinical and laboratory data, and bone marrow biopsies. Cases were interviewed during a hospital admission by trained interviewers using a structured questionnaire. Detailed information about demographic characteristics, use of medicines in the 6 months before admission, exposure to environmental factors and toxic agents, clinical status, laboratory data, treatments received, and events at follow-up was collected.

The severity of aplastic anemia was defined according to the widely accepted criteria described by Camitta.[14] Severe disease was defined as the presence in two of three blood counts of an absolute neutrophil count $<0.5\times10^9$/L, platelet count $<20\times10^9$/L, and reticulocytes <1%. Extreme neutropenia ($<0.2\times10^9$/L) defined very severe aplastic anemia.[15] All other cases were defined as moderate. Medical records were reviewed periodically in order to update clinical data (death, lost to follow-up, misdiagnosis, transfer to another medical center). The last follow-up was in December 1999. The results are, therefore, presented as follows: (i) incidence figures refer to cases diagnosed up to December 2003; (ii) survival analysis includes only patients diagnosed up to December 1999 since the last update on follow-up ended at that time, and (iii) case fatality rates at 2 years refer to cases diagnosed up to December 1997, since the patients had to be followed for at least 2 years. A 2-year disease-associated fatality rate has been used to estimate incidence rates from mortality statistics in population-based studies.[8]

Population data for incidence estimations were drawn from the National Census (*Institut d'Estadística de Catalunya [IDESCAT]*). Overall and specific incidence rates were calculated.

Statistical analysis

Descriptive statistical analyses (rates, proportions, and medians) were carried out using the SPSS version 11.0 software package. Confidence intervals were estimated with CIA software.[16] Rates and proportions were com-

pared with χ^2 tests. Survival probabilities were estimated using the Kaplan-Meier method, and comparisons between curves were based on the log-rank statistics. Analysis of risk factors for survival at 2 years was performed with Cox proportional hazards regression. Variables included in the multivariate model were age, sex, degree of severity, year of diagnosis and type of treatment received (bone marrow transplantation, immunosuppressive regimens, androgens).

Results

Up to December 2003, there were 507 patients identified as potential cases of aplastic anemia. Of these, 272 were excluded, leaving 235 confirmed cases for analysis (123 males, 52.3%). The most frequent reasons for exclusion were malignant neoplasm of blood-forming tissues and the lymphatic system (28.3%) (*http://www.icf.uab.es/aplasticanaemia*). The median age of patients at diagnosis was 53 years (95% confidence interval [CI] 44–58; range, 2-90). The median age of males was 40 years (95%CI 31–55; range, 2-90) and that of females 59 (95%CI 49-64; range, 3-90). The median time of follow-up was 1 year (range, 0-18.76, interquartile range 6.31). Twenty-eight patients (14%) were lost to follow-up and the clinical records could not be found for 21 patients (11%).

Incidence of aplastic anemia

During a study experience of 100,197,224 person-years, 235 cases of aplastic anemia were identified and confirmed, giving an overall incidence of 2.34 per million inhabitants per year (95%CI 2.06–2.66) (*http://www.icf.uab.es/aplasticanaemia*). Table 1 shows the specific incidence rates (SIR) according to age and sex. The sex-specific incidence rates were 2.54 for males and 2.16 for females (ratio 1.18; 95%CI 0.91–1.52). A biphasic age distribution with peaks at 15-24 years (2.16 per million per year) and ≥65 years (5.33 per million per year) was seen.

Cases of severe aplastic anemia

Out of the 235 cases, 197 fulfilled the criteria for severe or very severe aplastic anemia (83.8%; 95%CI 78.6–88.0). There were differences in severity when age was taken into account (p=0.027): the highest proportions of very severe aplastic anemia were seen among patients between 45 and 64 years old, and among those 2 to 14 years old (59.3% and 48.3%, respectively (*http://www.icf.uab.es/aplasticanaemia*).The proportion of cases with very severe aplastic anemia at the time of diagnosis decreased throughout the study period (p<0.005) (*http://www.icf.uab.es/aplasticanaemia*).

Case fatality, survival, and mortality

Among the 196 cases of aplastic anemia diagnosed between 1980 and 1999, the survival rate was 73% at 3 months, 57% at 2 and 5 years after diagnosis, and 51% at 15 years (Figure 1). Patients diagnosed after 1990 had higher survival rates at 2 years (p=0.018) (Figure 2A). Survival rates at 2 years after diagnosis were lower in patients over 45 years old than in those under 45 years old (p=0.0001) (Figure 2B). Although survival rates in males were higher than in females, no statistically significant differences were seen (p=0.38) (*http://www.icf.uab.es/aplasticanaemia*). Survival rates were lower in patients with severe disease (p=0.001) (Figure 2C). Of the 196 cases diagnosed with aplastic anemia between 1980 and 1997, 107 (68.2%) received immunosuppressive drugs, 19 (12.1%) androgens, 17 (10.8%) bone marrow transplantation, and 14 (8.9%) did not receive any treatment. It is not known for 39 patients whether they received any treatment or not (Figure 2D).

A Cox proportional hazards model on survival showed that more severe disease and advanced age were associated with a higher mortality rate at 2 years. The type of treatment did not show any statistically significant effect, but there was a trend for better survival in the small group of patients treated with bone marrow transplantation and a negative trend for those who received androgens (Table 2).

Table 1. Incidence of aplastic anemia according to age and sex.

	Age at diagnosis (years) 2-14	15-24	25-44	45-64	≥65	N. of cases	Total incidence[a]
Male							
N. of cases	17	25	22	28	31	123	
Incidence	1.92	2.83	1.52	2.56	5.89		2.54
Female							
N. of cases	12	11	15	31	43	112	
Incidence	1.43	1.41	1.00	2.58	4.89		2.16
Total							
N. of cases	29	36	37	59	74	235	
Incidence	1.68	2.16	1.26	2.57	5.33		2.34

[a]*Number of cases per one million people per year.*

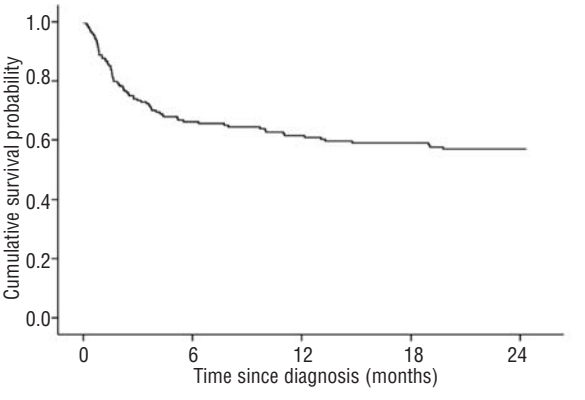

Figure 1. Cumulative survival probability of patients with aplastic anemia.

Out of 179 cases diagnosed between 1980 and 1997, 74 (41.3%) died within 2 years after the diagnosis (36 males, 48.6%). The median age of patients at death was 63.5 years (range, 10 to 87). Of the 74 patients who died, 47 (63.5%) had presented with very severe aplastic anemia, 24 (32.4%) with severe anemia, and three (4.1%) with moderate aplastic anemia. The overall case fatality rate at 2 years was 41.3% (34.4-48.7), and the mortality rate was 0.95 (0.75-1.19) cases per million inhabitants per year. Both increased with age (Table 3).

Exposure to drugs and environmental agents

Out of the 235 cases with exposure data, 67 cases (28.5%) had been exposed to drugs or toxic agents. Forty-nine (20.8%) cases had been exposed to the following drugs which have been reported to be associated with aplastic anemia:[8] allopurinol (n=9), indomethacin (n=9), gold salts (n=9), sulfonamides (n=9), butazones (n=6), carbamazepine (n=5), ticlopidine (n=4), chloramphenicol (n=3), penicillamine (n=3), methimazole (n=2) and clopidogrel (n=2). In addition, 21 (8.9%) cases had been exposed to toxic agents: insecticides (n=8), benzene (n=6), and other solvents (n=10) (*http://www.icf.uab.es/aplasticanaemia*).

Discussion

We report incidence estimations and survival rates of patients with aplastic anemia based on one of the largest series of such patients, with a very long period of follow-up. The overall incidence of aplastic anemia in the study area was 2.34 cases per million population per year, and the mortality at 2 years was nearly one death per million per year. Both increased with age. Survival rates were 73% at 3 months, 57% at 2 and 5 years, and 51% at 15 years. The prognosis improved over the 23-year period of the study. Young age and less severe disease at diagnosis were also associated with a better prognosis at 2 years. Patients treated with bone marrow transplantation showed a trend for better survival at 2 years.

The incidence of aplastic anemia in the metropolitan area of Barcelona was similar to that found in other population-based studies, such as the IAAAS (carried out in different European areas, and Israel),[8] and studies in France,[6] United Kingdom,[5] and Brazil.[7] However, it was lower than that reported for Asian countries,[17] and China.[18] Older studies generally provided much higher incidence figures.[9,11] These differences in incidence rates should be interpreted with caution because they can reflect method-

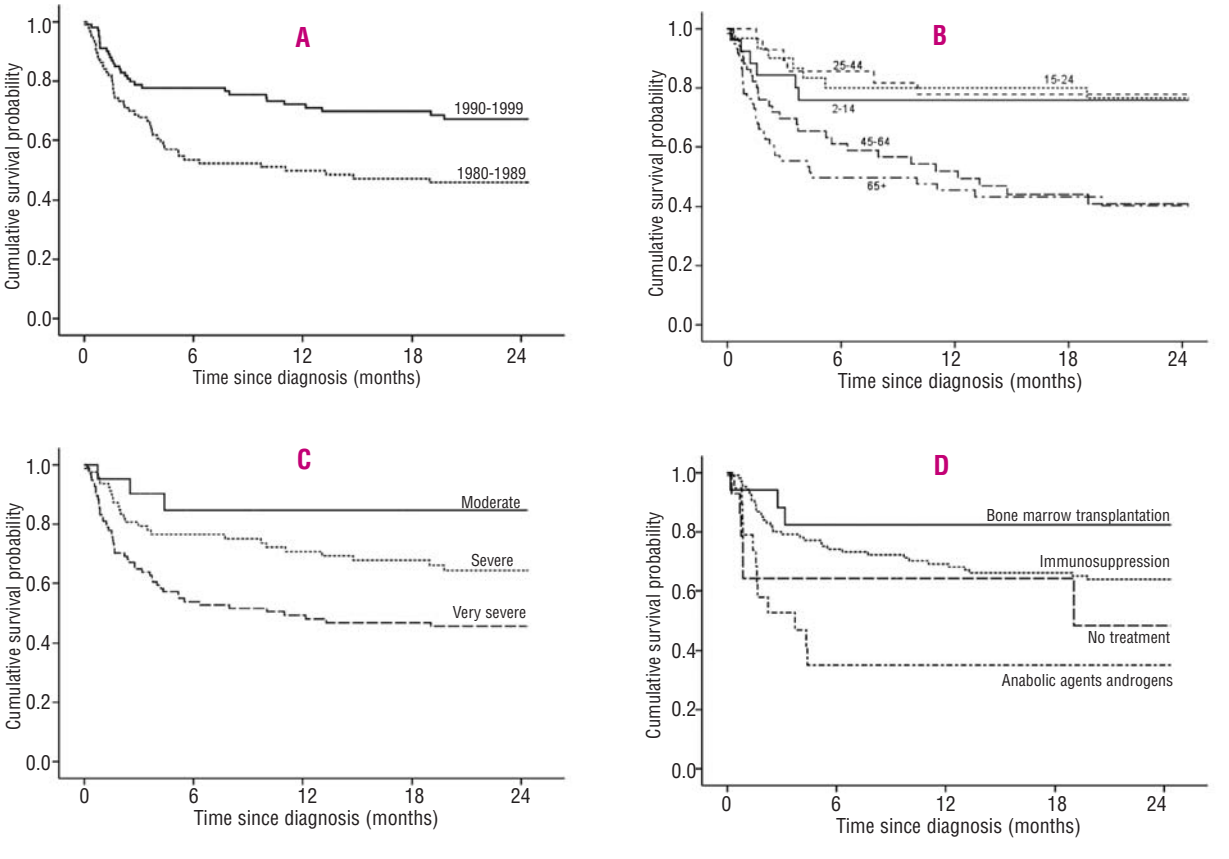

Figure 2. A. Effect of the year of diagnosis of aplastic anemia on cumulative survival probability. **B.** Effect of patients' age on cumulative survival probability. **C.** Effect of the severity of aplastic anemia on cumulative survival probability. **D.** Effect of treatment of aplastic anemia on cumulative survival probability.

ological variability in the ascertainment of cases and diagnostic criteria, although they could also be related to several factors such as genetic background and varying exposure to environmental factors.

We did not find any marked differences in the incidence of aplastic anemia by sex, and we recorded a bimodal age incidence. This is in agreement with the results of several population-based studies.[6,8] However, the IAAAS reported a somewhat higher incidence among females (2.3 per million per year) than among males (1.7 per million per year).[8] Moreover, in Thailand male cases were almost twice as frequent as female cases, and it was found that aplastic anemia was mainly a disease of young adults: a peak was observed among subjects 15-24 years old and the incidence in this age group was almost 4-fold higher than that in Europe and Israel. An environmental etiology was suggested.[12]

In our study, more than two thirds of cases were diagnosed as having severe or very severe disease. This proportion is similar to that found in other studies.[6,19] The proportion of severe cases at the time of diagnosis decreased throughout the study period, probably due to earlier diagnosis.

The survival curves in aplastic anemia were biphasic, i.e., rapid early mortality followed by a much slower decline. Survival rates fell from 73% at 3 months to 57% at 2 years, and remained 51% at 15 years. Survival figures from several series have shown the same biphasic curves, with the highest mortality rates within the first 6 months after diagnosis.[20-22] Five-year survival rates have been described to range from 70% to 90% and to be similar among patients treated with either bone marrow transplantation or immunosuppression.[24] In the early 1930s aplastic anemia was considered almost inevitably fatal. However, the morbidity and mortality of this disease have decreased dramatically since the introduction of bone marrow transplantation and immunosuppressive therapy.[24] In our study, the overall case fatality rate was 41% at 2 years after diagnosis, but it decreased from 50.5% in the first 10 years of the study period to 31% in the last 10 years.

The prognosis of patients with aplastic anemia has been related to several factors.[1] In addition to the period of diagnosis, the only factors that predicted survival were age and disease severity. The age-dependent survival rate in our study is in agreement with data from the International Bone Marrow Transplantation Registry[13,25] and with the findings of the IAAAS.[8] There were no statistical differences in survival at 2 years according to the type of treatment received. However, most patients received immunosuppressive therapy and the number of patients treated with other therapies was small. Bone marrow transplantation and immunosuppression have specific advantages and drawbacks but produce similar long-term survival rates.[1]

Table 2. Factors associated with death at 2 years after diagnosis.

	Hazard ratio	*95% confidence interval*
Age (years)		
2-14	1*	
15-24	1.34	0.33-5.37
25-44	1.22	0.27-5.51
45-64	3.41	0.97-11.91
≥65	5.50	1.56-19.02
Disease severity		
Moderate	1*	
Severe	4.57	1.06-19.73
Very severe	6.31	1.49-26.78
Year of diagnosis		
1990-1999	1*	
1980-1989	1.68	0.95-2.97
Treatment		
None	1*	
Bone marrow transplantation	0.47	0.11-2.12
Immunosupressive drugs	0.72	0.30-1.78
Androgens	1.30	0.45-3.72

**Reference category.*

Table 3. Case fatality rate and mortality at 2 years after diagnosis in patients with aplastic anemia according to patients' age.

Age (years)	*Number of cases*	*Number of deaths*	*Case fatality rate (%)*[a]	*95% CI*	*Overall case fatality rate (%)*[b]	*95% CI*	*Mortality (n/million inhabitants-year)*	*95% CI*
2-14	24	6	25	(12.0-44.9)	8.1	(3.8-16.6)	0.44	(0.16-0.97)
15-24	30	7	23.3	(11.8-40.9)	9.5	(4.7-18.3)	0.52	(0.21-1.06)
25-44	23	4	17.4	(7-37.1)	5.4	(2.1-13.1)	0.18	(0.05-0.45)
45-64	47	25	53.2	(39.2-66.7)	33.8	(24-45.1)	1.40	(0.91-2.07)
≥65	55	32	58.2	(45-70.3)	43.2	(32.6-54.6)	3.10	(2.12-4.37)
Total	**179**	**74**	**41.3**	**(34.4-48.7)**	**100**		**0.95**	**(0.75-1.19)**

[a]Case fatality rate for each age category; [b]case fatality rate related to the overall number of deaths for all age categories.

It is also worth mentioning that one third of the cases were exposed to drugs or toxic agents known to be associated with the disease.

Three major population-based studies of aplastic anemia have been reported; the IAAAS, the French Cooperative Group Study, and the Thai Aplastic Anemia Study.[6,8,12] We used identical methods to those of the IAAAS and Thai studies. However, in contrast to these previous studies, cases were recruited and followed-up over a longer period of time. The incidence figures are fairly reliable since all the important hospitals in the region participated, and efforts were made to include all the cases prospectively through close contact with hematologists. It is, therefore, unlikely that we missed a significant proportion of cases. Although diagnostic methods have improved recently, the incidence rates remained stable over the study period.

One of the limitations of our study is that we obtained the follow-up information from clinical records. As a result we could have missed some information when clinical records could not been found, as happened for 21 patients (11%).

In conclusion, the present study shows that aplastic anemia is a rare disease. Although the prognosis has improved significantly, the mortality rate among patients with this disease is high. The incidence and survival rates were similar to those in other European countries. Factors associated with death at 2 years after diagnosis were age over 45 at diagnosis, and very severe initial aplastic anemia. In addition, the fatality rate of cases diagnosed during the 1980s was higher than that in cases diagnosed in the 1990s. Further studies are needed to explore the role of risk factors on the prognosis, and the relevance of exposure to various chemicals, viruses and drugs as possible etiological factors.

Authorship and Disclosures

EM: analysis and interpretation of data; drafting the article and final approval of the version to be published; LI: conception, design and interpretation of data; drafting the article and final approval; XV: analysis and interpretation of data, revising the article and final approval; EB: acquisition, analysis and interpretation of data; revising the article and final approval; RP: analysis and interpretation of data; revising the article and approval of the final version; JRL: conception, design and interpretation of data; revising the article and approval of the final version.

The authors reported no potential conflicts of interest.

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