Epidemiology of Haemophilia in Greece: An Overview

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Summary

Demographic data of the Greek haemophilia A and B population for the period 1972–1993 were analyzed Prevalence at birth including known not-registered patients was calculated at 23 1 per 100,000 male births However, the observed prevalence in 1993 was only 61% of the expected Since 1975 the proportion of mild cases had significantly increased Adjusted by age, severity and HIV status reproductive fitness of haemophiliacs was 0 62 Overall mortality was 2 6 times higher than in the general population, but 7 9 times among patients with severe haemophilia and 16 4 among HIV(+) haemophiliacs Fifty out of 78 deaths occurred among HIV(+) patients and 28 of these were caused by AIDS Inhibitor patients did not show excess mortality due to bleeding Cancer mortality was equal to normal, but the number of deaths from ischaemic heart disease was 0 25 of the expected Risk of death due to cerebral haemorrhage was 3 8 times higher in HIV(+) haemophiliacs than in HIV(–)

Introduction

The Haemophilia Treatment Centre of Laikon Hospital (HTCLH), Athens, provides care for 72% of Greek haemophilia A and 81% of Greek haemophilia B patients (1) and is one of the largest European haemophilia centres This survey with information about 531 patients and their families covers a twenty-one-year period (1972–1992) and has the aim to estimate the prevalence of the disorder, the reproductive fitness of haemophiliacs and the mortality and causes of death of this group In the mortality figures, the impact of HIV infection is described

It is important to note that since 1960 Greek haemophiliacs have started to be treated systematically with fresh-frozen plasma Lyophilized cryoprecipitate of national origin was introduced in 1969 and PPSB in 1973 Factor VIII and later Factor IX concentrates were initially imported only for major surgery and since 1980–81 for routine use In September 1985 virus inactivated concentrates replaced all previous products Intermediate and high purity concentrates as well as FVIII purified by monoclonal antibody techniques are now used for substitution therapy During the last 5 years of the study the mean FVIII consumption was 12,500 IU annually per haemophiliac (24,000 IU for actively treated patients) Home treatment started eversince 1972 and it was spread to all patients that would benefit from it during the study period Finally, it is noteworthy that prophylactic treatment has never been used routinely in our centre (1)

The observed increasing prevalence of haemophilia, the increased patients average age and the changes in the death causes are factors that reflect the achievements of the last decades in the management of haemophilia and would be helpful if taken under consideration for planning of future haemophilia care

Patients and Methods

Prevalence

In estimating the prevalence at birth one has to account for underestimating because of deaths and delayed diagnosis (2) A first approach is to prepare a curve of the actual prevalence (number of living patients/number of living males) in all age groups, which will show a plateau in the first decades of adult hood This will yield a fair estimate if excess mortality is not too high, but will still be an underestimate Here we attempted a direct approach we searched to count all patients born in the period 1952–1976, and divided the final number by all males born in this period in Greece This period, with patients now ranging in age from 15 to 40 (if still alive) was chosen to minimize the effects of delays in diagnosis and registration before age 15, and of high excess mortality in older patients First, we made a table of all our registered patients (dead and alive) born in this period Subsequently we conducted family studies in 148 pedigrees to identify unregistered patients (dead or alive) which showed that our registry had a completeness of 85% in haemophilia A and 81% in haemophilia B In addition, we know that 28% of haemophilia A, and 19% of haemophilia B patients are registered in other centres Finally, with these figures we extrapolated from the patients registered in our centre, to all patients born in Greece between 1952 and 1976 by a proportional extension The estimation of the observed prevalence was based on the same method, apart from the fact that in the table we included only patients alive in the beginning of 1993

Fitness

Data for 318 patients born in the period 1931–1970 were used for the estimation of the reproductive fitness of haemophiliacs The number of their offspring until 31 12 92 derived from family studies Haemophiliacs who died before reaching genetic maturity (under age 15) were included in the final fitness calculation since they represent haemophilic genes lost All patients were divided in three groups according to severity and in four subgroups according to the decade of their birth The mean number of children of the patients in each age group was compared to the expected number for that age group based on figures for the general male population (3) The ratio of the observed number of children summed over all age groups, and of the expected number summed over all age groups is the age-standardized fitness The observed number of children was adjusted for HIV-status and severity prior to this comparison, to allow for incomplete data in some of the patients seen less frequently [i e HIV(–) patients, mild haemophilia] and not included in the study Complete data on family size were available for 82% of our centre's patients Obviously, for various reasons HIV status and severity affect fitness

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Mortality, Life Expectancy, Causes of Death

The follow-up covers the period from 1-1-1972 to 31-3-1993 Sixty-two patients with mild haemophilia (mean FVIII C approximately 11 IU/dl) originating from the village Aiani of Macedonia and sharing the same mutation (4) formed a special category The patient-year method was used for the calculation of Standardized Mortality Ratios (SMR), which compare the observed to the expected number of deaths, based on the population mortality rates The expected mortality was adjusted for age, sex and calendar period The calculation of confidence intervals was based on a Poisson distribution Since for several reasons infant mortality in haemophiliacs may be underestimated (5, 6) we decided to exclude infant mortality in both patients and population figures Therefore, when registration year was the year of birth, entry in the study group was one year later The eight age groups used were 1–19, 20–29, , 70–79 and over 80 years old The same calculations were made for the group of HIV(+) patients starting from the approximate mean seroconversion date (1-1-1983)

The causes of death were in almost all cases certified by HTCLH physicians Autopsies were generally not performed Cause-specific mortality for deaths due to cancer and ischaemic heart disease were calculated with cause-specific population mortality rates Finally, after an initial observation of excess mortality due to cerebral haemorrhage of HIV(+) patients over HIV(–), we estimated the incidence of fatal cerebral bleeding in both groups adjusted for age and severity Patient-years for HIV(+) and HIV(–) status were calculated using 1-1-1983 as the seroconversion date for HIV(+) patients Obviously, these patients contributed patient-time to both HIV(–) patient-years (before 1-1-83) and HIV(+) patient-years (after 1-1-83) A Poisson regression model was used to estimate the incidence rate ratio for fatal cerebral bleeding in HIV(+) and HIV(–) status adjusted for age and severity The results were expressed as rate ratios, relative for each variable to the lowest (reference) category

Definitions

Patients were grouped by severity according to FVIII C or FIX C levels, severe clotting activity <1 IU/dl, moderate clotting activity 1–5 IU/dl, mild clotting activity 5–25 IU/dl Haemophilia B Leiden patients were considered as mild cases Von Willebrand disease was excluded by appropriate testing Coagulation measurements were performed by standard techniques We

Table 1 Prevalence at birth and observed prevalence of haemophilia in the Greek population

Type and severity	No of haemophilic infants born in the period 1952–76	Prevalence per 100,000 male births	No of haemophiliacs alive in 1-3-1993	Observed prevalence per 100,000 males
Severe	144	7 4	181	3 6
Moderate	54	2 8	108	2 1
Mild	178	9 2	317	6 3
A				
All	376	19 3	606	12 0
Severe	46	2 4	53	1 1
Moderate	12	0 6	27	0 5
Mild	14	0 7	21	0 4
B				
All	72	3 7	101	2 0

The prevalence at birth is calculated by the number of males born alive in Greece between 1952 and 1976 The total prevalence per 100,000 male births by severity is severe 9 8 (42%), moderate 3 4 (15%) and mild 9 9 (43%)
The observed prevalence is calculated according to the Greek male population in the 1991 census The total prevalence per 100,000 males by severity is severe 4 6 (33%), moderate 2 7 (19%) and mild 6 7 (48%)

Table 2 Reproductive fitness of haemophilia A & B patients by period of birth and severity

Severity	Period of birth	Patients/births	Ratio of births observed/expected	Fitness
S				
E	1931–1940	31/29	0 46	
V	1941–1950	24/20	0 42	0 37
E	1951–1960	50/21	0 30	
R	1961–1970	50/ 3	0 18	
E				
M				
O				
D	1931–1940	16/18	0 56	
E	1941–1950	13/ 9	0 38	0 41
R	1951–1960	14/ 5	0 24	
A	1961–1970	17/ 1	0 18	
T				
E				
M	1931–1940	29/59	1 01	
I	1941–1950	23/41	0 89	0 93
L	1951–1960	29/41	0 95	
D	1961–1970	22/ 2	0 28	

considered as registered only male patients with a known vital status including dates of birth and death, type and severity of haemophilia In this way about 5% of patients were excluded from the study for incomplete data

Results

At 1 3-93 there were 707 Greek haemophilia patients on a total population of 5 05 million Greek males, i e observed prevalence was 14 0 per 100,000 males – 12 0 in haemophilia A, 2 0 in haemophilia B (Table 1) Among these patients 619 were registered (453 in our centre and 166 elsewhere) and 88 (12%) were known not registered patients It also follows that observed prevalence of severe haemophilia was one out of 21,500 males The overall prevalence at birth was 23 1 per 100,000 male births, 65% higher than the observed prevalence This implies that one out of 5,200 males is born with haemophilia A and one out of 27,000 males with haemophilia B

Information about reproductive fitness for patients born before 1970 is given in Table 2 The overall fitness, standardized for age, was 0 62 (318 patients had 249 children, whereas 402 children were expected on population figures) For HIV(+) patients fitness was 0 47 Since 1987 none of the HIV(+) patients has reproduced The difference in number of offspring compared with the general male population was most pronounced for the younger generations (fitness by period of birth was for 1931–1940 0 67, 1941–1950 0 62, 1951–1960 0 55 and 1961–1970 0 21)

Table 3 General characteristics of patients of HTCLH registry (n = 531)

		N	(%)
Type			
	Haemophilia A	460	(87)
	Haemophilia B	71	(13)
Severity			
	Severe	212	(40)
	Moderate	92	(17)
	Mild[1]	227	(43)
HIV status[2]			
	(+)	156	(29)
	(–)	375	(81)
Inhibitor[3]			
	(+)	38	(7)
	(–)	453	(93)
Year of birth			
	1900–1930	50	
	1931–1940	61	
	1941–1950	77	
	1951–1960	121	
	1961–1970	90	
	1971–1980	97	
	1981–1991	35	

[1]62 patients with mild haemophilia had a common ancestor originating from the village Aiani of Macedonia Four patients are haemophilia B Leiden

[2]HIV seropositivity is much lower among haemophilia B patients (8%) and differs considerably by severity (severe 62%, moderate 28%, mild 8%)

[3]No haemophilia B patient developed inhibitor and only 14 patients (3% of the haemophilia A population) out of 38 were high responders, i e developed non transient inhibitors (anamnestic response with titres over 10 BU/ml)

Concerning mortality, we followed 531 individuals (the general characteristics of that population are described in Table 3) for a total of 8641 person-years We observed 78 deaths (Table 4), while 30 were expected based on age and sex adjusted population rates [SMR 2 6 with 95% confidence intervals (C I) of 2 1 to 3 3] Mortality was almost 8 times higher in patients with severe haemophilia than in the general population and the majority of deaths – 54 – occurred among patients of this group On the contrary, patients with mild and moderate haemophilia did not experience excess mortality (SMR about 1) Mortality was by far the highest in HIV(+) haemophiliacs after the mean date of infection (SMR 16 4) Of the 78 deaths in our cohort, 50 occurred in HIV(+) patients [32% of the 156 HIV(+) patients had died] It should be emphasized that among HIV(–) patients with moderate and mild haemophilia we observed no death under the age of 48 and among the 62 patients originating from the Aiani village only one patient had died The mean age of death of our patients was 44, while in severe haemophilia it was 39 and in mild haemophilia 53 Life expectancy for HIV(–) patients appeared to be almost normal

The most common cause of death among our patients was AIDS (Table 5) Cerebral haemorrhage followed in frequency and was the commonest cause among HIV(–) patients Other types of bleeding were responsible for only 8 deaths Among the 38 inhibitor patients only one high responder died from bleeding in 1983 However, 7 more patients of this group died due to viral diseases (five by AIDS, two by liver diseases) SMR for deaths due to malignancies was 0 83 with 95% C I of 0 3 to 1 8 Only one patient died due to ischaemic heart disease instead of four expected Consequently, the SMR for that cause was 0 25 with 95% C I of 0 0 to 1 4

The mortality by cerebral haemorrhage was found 5 0 times higher in HIV(+) than in HIV(–) haemophiliacs, i e 8 in the 7210 patient-years of the HIV(–) group and 8 in the 1431 patient years of the HIV(+) group The incidence of death by cerebral bleeding was almost the same – 5 5 per 1,000 patient years – in all three severity groups among HIV(+) haemophiliacs, while in HIV(–) patients it varied from 0 4 in mild cases to 1 6 in moderate and severe Since the HIV(+) patients differed in severity of haemophilia and age distribution from the HIV(–) patients, we adjusted for these variables by multivariate Poisson regression This showed that each increase in severity (mild to moderate, moderate to severe) doubled the risk of death from cerebral haemorrhage (Table 6), while each 10-year increase in age led to 1 5 increased risk Most importantly, after this correction, the risk of HIV(+) individuals still was 3 8 times as high as for HIV(–) patients

Discussion

It is obvious that the results of this study are much coloured by HIV infection The moderate use of imported commercial concentrates on one hand and the persistence in strictly providing "on demand" substitution therapy on the other, have resulted in a medium number of seropositive patients in Greece (29%) compared to Germany (53%), France (50%) and United Kingdom (39%), where higher prevalences of HIV antibodies among haemophiliacs have been observed (7–9), and to The Netherlands (17%), Belgium (4%) and Finland (1 5%), where the predominant use of plasma products from local nonpaid donors (10, 11) explains the low numbers of infected patients Of course, the percentages given are not completely comparable since different methods have been applied for the calculations

A comparison of the present study with a report for the Greek haemophilia population in 1975 (12) shows a considerable increase in the observed prevalence of haemophilia (14 0 versus 8 6 per 100,000

Table 4 Mortality by severity and HIV status

Group		Patient years (yrs)	Standardized mortality ratio[1]	95% confidence intervals	Number of deaths
ALL	Severe	4072	7.9	6.0–10.4	54
	Moderate	1565	1.2	0.6–2.2	11
	Mild	3003	0.9	0.5–1.6	13
	Total	8641	2.6	2.1–3.3	78
HIV(+)	Severe	1010	17.9	12.7–24.5	39
	Moderate	256	14.7	4.8–34.3	5
	Mild	175	11.4	4.2–24.6	6
	Total	1443	16.4	12.2–21.6	50

[1]Expected mortality based on national Greek mortality rates of 1970, 1975 1980 and 1985 in 5 years age classes Therefore, rates are adjusted for age, sex and calendar period

Table 5 Causes of death of HTCLH registered patients between 1 1 1972 and 31 3 1993

Cause of death	N	N of HIV (+)
AIDS	28	28
Cerebral haemorrhage	16	8
Bleeding	8	2
Liver diseases	6	5
Cancer	6	2
Heart diseases	4	3
Other[1]	6	2
Unknown	4	0
Total	78/531	50/156

[1]Pneumonia 2, diabetes 1, encephalitis 1, renal failure 1, suicide 1

Table 6 Poisson regression analysis of cerebral haemorrhage deaths

Variable	Rate ratio	95% confidence intervals
Mild	1.0[1]	–
Moderate	2.6	0.4–15.4
Severe	3.9	0.8–19.6
Age group[2]	1.5	1.2–2.0
HIV status[3]	3.8	1.3–10.7

[1]Reference category
[2]10 year age groups
[3]HIV (–) as reference category

males), but a slight reduction (from 5.1 to 4.6) among severe patients, probably due to the AIDS epidemic and the satisfactory registry in this group, already by 1975 On the contrary, the rapid growth of mild patients population (from 2.0 to 6.7) is a result of increased registry and reduced mortality Mild haemophiliacs now represent almost half of the total number of patients compared to 23% in 1975 A similar development was observed in Sweden (13) between 1960 and 1980 (from 35% to 54%) The total prevalence at birth (23.1 per 100,000 male births), is close to 20.6 calculated for the Dutch population (2) and to 17.8 resulting by application of the plateau method to Swedish data (13) Our estimation is slightly higher, which may be explained by our efforts to include known, not registered patients by family studies, which was not attempted in the other studies Without this correction, our estimation becomes 19.5 per 100,000 The calculation of prevalence at birth requires extrapolations that will have introduced some error It is likely that, despite all efforts, some patients were not counted, e.g. those who were never diagnosed Therefore, we still think this estimate to be a slight underestimate

If the same prevalence as at birth was observed in each age group, the Greek haemophilic population, which is now estimated at 707 patients, would have consisted of 1161 individuals The deficit of 39% is higher than the reported from The Netherlands (22%) and Sweden (23%) (2, 13) Several explanations may be offered i) Even elementary haemophilia care started to be provided in Greece later than the most Western European countries, which may have led to higher deficit in older age groups because of early deaths ii) Many patients are still not registered, which deprives them from specialist care iii) Deaths due to AIDS (not included in the previous studies) iv) More women in Greece tend to choose for prenatal diagnosis and selective abortion than Dutch and British women (2, 14) Greek women are more accustomed to the idea of "pregnancy termination", because of the high prevalence of thalassaemia heterozygotes and the legalization of abortion ten years ago Generally, it seems that the deficit between observed prevalence and prevalence at birth will not be eliminated in the Greek population (leading to a significant increase in the number of haemophiliacs) so soon as was foreseen for the Dutch haemophiliacs (2) An additional reason for that is the higher HIV(+) percentage, not so much as a cause of a temporary increased excess mortality, but because of its effects in the reproductivity of our population, which may reduce on a long term basis the number of obligate carriers Conclusively, no increase of haemophilia prevalence is expected for the following decades, while the percentage of mild patients will continue to grow

Since 1947, when Haldane (15) calculated fitness of haemophiliacs to be 0.28, several studies have been published on that subject According to Francis and Kasper (16) haemophiliacs with clotting activity less than 2% of the normal showed in the period 1940–1977 a reproduc-

tivity rate 43% of the expected We found a fitness of 0 62 for Greek haemophilia patients born after 1930 This may reflect improvement in care in recent periods Cultural differences are also important, e g the patient's view concerning the birth of daughter carriers Lately, a Hungarian study (17) has reported a fitness of 0 3 for haemophilia A and 0 8 for haemophilia B, which was, however, based on a relatively small number of patients In The Netherlands fitness for living haemophilia patients was 0 70 (18), similar to the present study if patients who died under 15 would have been excluded Finally, the lower fitness of the younger generations may be explained by the influence of the HIV infection in haemophiliacs reproductivity after 1986, as well as by their delay in the age of marriage (16, 17)

Before the introduction of substitution therapy the cause of deaths among haemophiliacs was, almost unvariably, bleeding The low number of deaths due to all types of bleeding, except cerebral haemorrhage, in this study proves the improvement in the effectiveness of the provided care Nowadays, haemophiliacs are growing older and survive to experience diseases of the elderly like cancer and ischaemic heart disease However, these have not yet become the commonest death causes because of the appearance of transfusion transmitted viral diseases Already from 1975, 77% of polytransfused Greek haemophiliacs were infected by the hepatitis B virus (12) and 47% had abnormal liver function tests (19) In the present study 8% of deaths were reported to be caused by liver diseases, giving cause to the fears expressed in previous studies (5, 20) Additionally, since haemophiliacs infected by HIV, HBV and HCV are not uncommon (21), more deaths due to combined infections may be expected for the near future

It has been previously reported (20, 22, 23) that patients with antibodies have a higher risk of dying due to bleeding than patients without antibodies In this study, however, it seems that this is not the case Suicide was the cause of death for 5% of both British and Dutch haemophiliacs (20, 23), while a high percentage was also reported from the USA (6) We report only one suicide of a 34-years-old schizophrenic patient This may reflect a low suicide rate in the Greek general population Cause specific SMRs reveal that no excess mortality due to malignancies is observed among Greek haemophiliacs, which is in good agreement with other published studies (6, 20) as well as with a recent survey in Dutch haemophiliacs for the period 1986–1992 (unpublished data) Previously a substantial reduction (by 80%) of deaths due to ischaemic heart disease was found in Dutch haemophilia patients (23), which could not be explained by differences in the presence of major classical risk factors (24) The conclusion that haemophilia and the related clotting defect offer protection against ischaemic heart disease is supported by the present results in the Greek patients Cerebral haemorrhage accounted for 29% of deaths among HIV(–) patients of this study, which is similar to the figure found in the United Kingdom (20) Among HIV(+) haemophiliacs, however, the risk of fatal cerebral bleeding appears to be much higher

The intention of this study was to estimate the past, realize the present and plan the future, as well as to provide a baseline for forthcoming comparative studies in the Greek haemophilia population No more than a decade ago, the indisputable improvements in haemophilia management would have led similar studies to optimistic predictions However, the shadows of viral infections permit at the present only modest expectations, probably combined with well founded feelings of hope

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