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Changes in the life expectancy of patients with severe haemophilia A in Finland in 1930–79

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SUMMARY. Important advances have been made in the treatment of haemophilia during the past 30 years. We have analysed the data of all the known 163 patients with severe haemophilia A living in Finland in 1930–79 in order to study changes in the prognosis of severe haemophilia A. During the period of 50 years the mean age at death of the patients has increased from 7·8 years in 1930–39 to 25·5 years in 1970–79 and the annual death rate has markedly decreased in all age groups. The decline has been greatest in patients under 10 years of age. In this age group the annual death rate decreased from over 50 per thousand in 1930–39 and 1940–49 to 4·8 per thousand in 1970–79. The prognosis of patients with inhibitors has remained poor, however. Five of the six deaths during the last decade occurred in patients with inhibitors. The overall annual death rate of patients without inhibitors was only 1·2 per thousand in 1970–79, suggesting that at the present time the life expectancy of patients who do not develop inhibitors does not markedly differ from that of the general male population.

Blood transfusion was first employed in the treatment of haemophilia by Lane in 1840 but it was not utilized to any significant extent until about a hundred years later and then it rapidly became the mainstay of treatment. The use of fresh-frozen plasma in haemophilia A was a further step forward but during the last 20 years the wider availability of concentrates has revolutionized treatment. There seems to be no doubt that this progress in treatment has greatly improved the outlook for patients with severe haemophilia A.

In Finland more active use of fresh-frozen plasma was adopted during a survey made in 1957–59 (Ikkala, 1960). Cryoprecipitate was introduced in 1967 and adequate amounts of lyophilized cryoprecipitate made of 2–8 units of pooled plasma have been available since 1969. A register of Finnish haemophiliacs was started in 1957–59 and was checked in a new survey of living haemophiliacs in 1978–79. The present report is based on this register and

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concerns changes in the life expectancy of patients with severe haemophilia A during the 50-year period 1930–79.

SERIES AND METHODS

The series consists of 163 patients with severe haemophilia A, 125 of whom have been examined in the haemostasis laboratory of the Finnish Red Cross Blood Transfusion Service and 38 are deceased bleeders belonging to the families of known bleeders. On 31 December 1979 the number of living patients was 100, that of deceased bleeders 59, and the fate of four patients who had emigrated was unknown. Our laboratory is the only specialized haemostasis laboratory in Finland and samples of all patients suspected of having coagulation defects are sent to us. Thus the series includes all known patients with severe haemophilia A in Finland. The methods used for the collection of information about deceased haemophiliacs have been described earlier (Ikkala, 1960).

In 1956–63 the classification by severity of patients with haemophilia A was made with an assay based on the thromboplastin generation test with some corrections according to the results of global tests (Ikkala, 1960). Since 1964 the classification has been based on the kaolin–cephalin time (APTT) method using the plasma of severe haemophilia A patients as substrate (Hardisty & Macpherson, 1962); patients with factor VIII activity below 1 u/dl have been classified as severely affected. In the second survey 54 patients of the first survey were restudied and one patient originally classified as having moderate haemophilia A was reclassified to the group of severe haemophilia A.

In 1957–59 factor VIII inhibitors were found in one patient by a simple recalcification method (Ikkala, 1960). Since then inhibitors have been found in 16 additional patients by the Oxford (Biggs & Bidwell, 1959) and Bethesda (Kasper *et al*, 1975) methods. The fate of one emigrant patient is unknown.

The home therapy programme was started in Finland in 1973 and 30 patients have been on this therapy for 6 months to 6 years (median 3 years). Prophylactic treatment with infusions once or twice weekly has been given to 17 patients during 6 months to 12 years (median 4 years).

RESULTS

Of the 163 patients of the present series, 144 were born in 1930 or later. In 1930–74 the ratio of haemophiliacs born per liveborn males was 1:13500, varying in 5-year periods from 1:11000 (in 1945–49) to 1:19000 (in 1965–69). The birth rate of patients with severe haemophilia A has thus been quite constant. The number of living patients, however, has increased from 67 in 1957 to 100 (four emigrant patients excluded) in 1979 and a definite change is seen in the age distribution (Fig 1). The mean age at death has increased from 7·8 years in 1930–39 to 25·5 years in 1970–79 (Table I). A list of the causes of death before and after 1960 (Table II) shows that originally simple bleeding had caused only one death since 1960. It should be noted, moreover, that five of the six patients who died after 1970 had factor VIII inhibitors.

The annual overall death rate decreased from 39·2 and 53·3 per thousand in 1930–39

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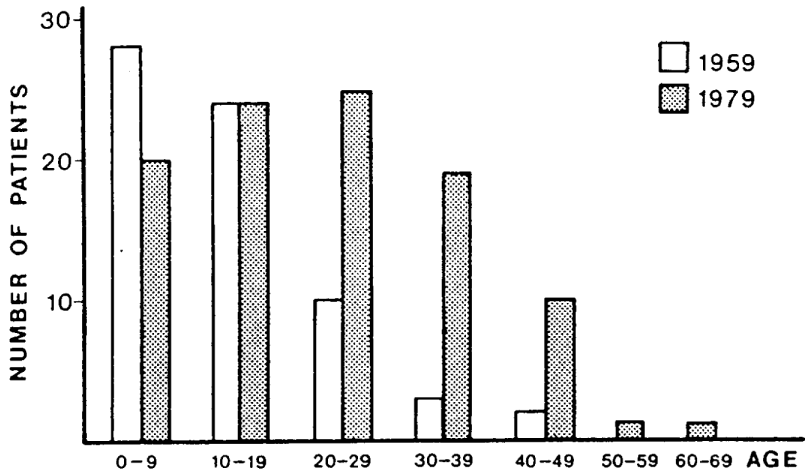

Fig 1. Age distribution of living patients with severe haemophilia A in 1959 and 1979.

and 1940–49, respectively, to 6·5 per thousand in 1970–79. This change was mainly due to the decline in the death rate of patients below 10 years of age from over 50 per thousand in 1930–39 and 1940–49 to 4·8 in 1970–79 (Table III). The decrease was most marked in patients under 3 years of age, 18 of the 99 patients born in 1930–59 dying before this age whereas all of the 45 patients born in 1960–79 were living at the age of 3 years. Only 19 patients survived over 40 years. Among them there were five deaths per 51 years of life in 1930–69, but in 1970–79 there were no deaths per 82 years of life. Table III compares also the death rates of the patients with those of the Finnish male population (Central Statistical Office of Finland; personal communication). The decrease in the haemophiliac death rates clearly exceeds the changes in the male population deaths. The improvement in the prognosis of the patients is further illustrated by the survival curves for the first 40 years of life based on the death rates in 10-year age groups in periods 1930–59, 1960–69 and 1970–79 (Fig 2).

The outlook of patients with inhibitors has remained poor. Five of the 16 patients have died, all in 1970–79. In this period the annual death rate of this group of patients was 42 per

Table I. Mean age at death of patients with severe haemophilia A by 10-year periods in 1930–79

	1930–39	1940–49	1950–59	1960–69	1970–79
Mean age (years)	7·8	13·3	10·2	20·1	25·5
Range	1–40	0·01–51	0·5–31	1–52	8–39

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Table II. Causes of death in patients with severe haemophilia A in 1930–59 and 1960–79. In parentheses, number of patients with inhibitors.

Cause of death	No. of deaths 1930–59	1960–79
Wound, oral and subcutaneous bleeding	17	1
'Internal' bleeding	5	4 (3)
Gastrointestinal bleeding	6	4
Intracranial bleeding	5	7 (2)
Severe trauma		1
Other causes or unknown	8	1
Total	41	18 (5)

thousand (five deaths per 120 years of life). The removal of these patients from the analysis gives for the patients without inhibitors an overall annual death rate of only 1·2 per thousand.

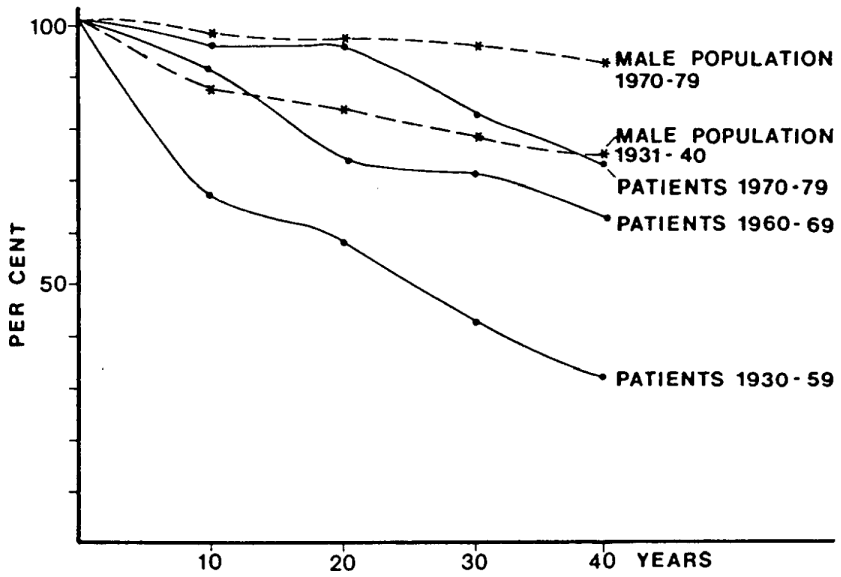

Fig 2. Survival curves of patients with severe haemophilia A based on annual death rates in 1930–59, 1960–69 and 1970–79 compared with those of Finnish male population in 1931–40 (war casualties excluded) and 1970–79.

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Table III. Annual death rate of patients with severe haemophilia A and of the Finnish male population in age groups 0–9, 10–19, 20–39 and over 40 years by 10-year periods in 1930–79

	Annual death rate per thousand (no. of deaths/no. of years of life)									
	0–9 years		10–19 years		20–39 years		>40 years		Total	
	Patients	Population	Patients	Population	Patients	Population	Patients	Population	Patients	Population
1930–39	56·3 (9/160)	13·3	0 (0/71)	3·4	21 (1/48)	7·0*	250·0 (1/4)	32·0	39·2 (11/283)	14·5
1940–49	54·5 (11/202)	12·2	34·4 (4/116)	3·0*	60 (4/67)	6·3*	222·2 (2/9)	30·5*	53·3 (21/394)	14·0*
1950–59	20·3 (6/295)	4·7	5·6 (1/177)	0·9	17 (2/119)	2·9	0 (0/13)	26·1	14·9 (9/604)	10·1
1960–69	10·5 (3/286)	2·7	19·2 (5/259)	0·8	8·1 (2/247)	2·5	80·0 (2/25)	28	14·7 (12/817)	10·3
1970–79	4·8 (1/210)	1·6	0 (0/258)	0·8	13 (5/380)	2·2	0 (0/82)	27·6	6·5 (6/930)	10·6

* War casualties excluded.

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DISCUSSION

We have been able to find only one report giving the exact data about changes in the prognosis of patients with haemophilia. Baker (1980) in analysing 70 deaths among patients with various types haemophilia in Denmark found that the mean age at death increased from 25·6 years in 1949–58 to 41·8 years in 1969–78 after having earlier been 18 years (Andreassen, 1943). We have restricted our analysis to the patients with severe haemophilia A instead of studying the whole haemophilic population. This is the largest and most homogeneous group among haemophiliacs, and developments in diagnostic facilities have had hardly any effect on the number of patients found, as may have been the case in milder forms of haemophilia.

The prognosis of severe haemophilia A was very poor before 1950 when about half of the patients died before the age of 10 years. Each of the following three decades showed a drop of about 50% in the death rate of this age group. The change was most marked in patients below 3 years of age, but it was clearly seen also in patients over 10 years of age. The drop in the decennial death rates concurred with, respectively, the increased use of blood transfusion, the use of fresh-frozen plasma and the availability of cryoprecipitate. The occurrence of only one death from simple bleeding after 1960 also emphasizes the role of replacement therapy. The improvement in the life expectancy of patients with severe haemophilia A cannot be attributed solely to developments in replacement therapy. During the past 30 years, especially, the standards of living and of medical care in Finland have greatly improved. Nevertheless the life expectancy of patients with severe haemophilia A has improved much more than that of the Finnish male population.

The increased use of blood products is, however, accompanied by an increase in the number of patients with inhibitors (Ikkala & Simonen, 1971). The outlook for these patients has remained poor, e.g. five of six patients who died during the last decade had inhibitors. The low death rate of patients without inhibitors in 1970–79 suggests that at the present time the life expectancy of patients with severe haemophilia A who do not develop inhibitors does not differ markedly from that of the general male population.

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The occurrence of classical haemopl difficult to achiev therapy for only t conservatively wit our policy has cha those without an rhage, but in lar consequence mar frequent injection accompanied by a patients with well of the antibody l although still pres We describe our

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excess of NTDs but is not included, as it is not clear whether the data overlap those of Fogh-Andersen's study.)

The only large series of probands with isolated cleft palate (CP) that reports the appropriate data is that of Fogh-Andersen;[8] 3 of 517 sibs of children with CP had a NTD, as compared with 0·8 expected (table II). In the Montreal series of 80 CP probands there were no sibs with proven NTD in 202 sibs (0·7 expected), and in the Hungarian registry there are 179 CP probands with no cases of NTD in 185 sibs. No conclusion can be reached until more data are available.

OTHER MALFORMATIONS

We have found three other studies that report the frequencies of other malformations in the sibs of children with a particular congenital malformation (table II). In London,[12] 3 of 162 sibs of children with exstrophy of the bladder had an NTD (0·5 expected) and 5/181 sibs of children from South West England with diaphragmatic hernia[13] had an NTD (0·7 expected). Thirdly, in a family study of renal agenesis[14] there were 4/195 sibs of probands who had NTDs (excluding one family where the proband also had an NTD). We note with interest a preliminary report, in which 6 of 250 sibs of patients with germ cell tumours had an NTD.[15]

COMMENT

The frequency of NTD thus seems to be increased in the sibs of probands with any one of five kinds of common malformation for which the appropriate data are available. In areas with relatively high frequencies of NTD (Great Britain, Quebec), the probability of NTD in the first-degree relatives of probands with one of these defects approaches or exceeds 1%, the level conventionally accepted as justifying prenatal diagnosis. The reason for the excess of NTD is not apparent. Several possible explanations come to mind. These include:

(1) *Sampling bias, reporting bias, or preferential selection* of series that show the association with NTD. This seems unlikely since several series were ascertained from health records rather than referrals to genetics centres. Also mendelian disorders did not show the increase, data were collected without reference to the possibility of an association, and no series of reasonable size that presents the relevant data has been excluded. Nevertheless, the possibility should be tested by well-controlled population-based studies.

(2) *Genetic heterogeneity.*—Each of the above groups of probands might contain a small admixture of cases with a recurrent syndrome, such as Meckel syndrome, that can result in one or more of the involved malformations in one child and an NTD in another. No evidence for this has been found in cases where the relevant details are available.

(3) *A diminished capacity of certain mothers to reject certain types of malformed embryos.*—Such a mother might fail to reject an embryo with TOD in one pregnancy and an embryo with NTD in another. NTDs, being the most frequent malformation would show the greatest increase in the offspring of such mothers. This would imply that the frequency of NTD in embryos is sufficiently high to account for the observed increases in NTD. This appears to be so. Of 173 embryos of less than 36 days old, 3 (1·7%) had an NTD in a country (Japan) where the frequency at birth is about 0·8/1000.[24]

(4) *A uterine, familial environmental, or genetic embryonic factor that increases the probability of various fusion defects.*—Which defect would occur in a particular embryo would depend upon that embryo's genetic predisposition. NTDs, being the most common of these and the one most influenced by environmental factors,[25] would be expected to show the most striking association. One of us has recently drawn attention to the association of schisis-type defects within patients, and the fact that the sibs of patients with multiple schisis-type defects may have schisis-type defects, usually NTD.[26] Perhaps we are observing the same thing here, namely that fusion type defects show association both within patients and within families. If the association also includes monozygotic twinning[27] this would explain the increase in twinning known in TOD,[28] and in NTD, and probably also in CL(P) and diaphragmatic anomalies.[29] The precipitating factor could be something that causes fetal growth retardation, as recently suggested by Spiers.[30]

Analysis of further well-documented population-based family studies may lead to identification of relevant genetic and environmental factors. If the association is real, prenatal diagnosis should be offered in subsequent pregnancies to mothers who have had a child with any defect that shows this relation to NTD.

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