Journal of Korean Medical Science
Vol.3, No.3, P107-115, September 1988

Comprehensive Clinical and Statistical Analysis of Hemophilia in Korea

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A Total of 498 cases of hemophilia which were reported by sixteen medical centers in Korea were reviewed and analyzed. Hemophilia A comprised 425 cases (85.3%) and the remaining 73 cases (14.7%) were hemophilia B. One case was female and all other cases were male. There were known hemophilia patients in the family in 43.0% of cases and the involved members were brothers, maternal cousins, maternal uncles, and maternal grandfathers in descending order of frequency. The major symptoms of the patients were hemorrhagic, such as easy bruising and hemarthrosis followed by prolonged bleeding after trauma and soft tissue hematoma. The incidence of hemarthrosis increased significantly with age. The pediatric age group below the age of 15 consisted of 67.1% of the cases. According to the age at diagnosis, half (54.2%) of the severe cases were diagnosed before the age of 1 year. APTT was prolonged over 40 seconds in all cases and 291 cases showed severe prolongation over 80 seconds. Of 498 cases 273 cases (54.8%) belonged to the severe form (factor VIII or IX level, less then 1%), whereas 182 cases (36.5%) and 43 cases (8.7%) belonged to the moderate (factor VIII or IX, 2-5%) and mild form (factor VIII or IX, 6-25%), respectively, Chronic arthropathy was present in 236 cases (49.6%), and the incidence increased significantly with age. The management of chronic arthropathy most commonly employed was rehabilitation in 25.4% of cases, but in 50.8% no management was given at all. The involved joints in descending order of frequency were knees, elbows and ankles. The complications were intracranial hemorrhage, GI bleeding and nerve palsy in 48, 24, and 13 cases, respectively.

Key Words: *Hemophilia, Factor VIII deficiency, Factor IX deficiency, Clinical and Statistical analysis*

INTRODUCTION

Hemophilia is one of the hereditary hemorrhagic disorders which is transmitted through the sex (X)-linked recessive pattern. Since the 1970s, the availability of concentrated preparations of factor VIII and factor IX has greatly improved the lives of hemophiliacs. There have been considerable changes in treatment, such as the comprehensive care for hemophiliacs including rehabilitation and home therapy.

Despite these advances, the most important of which are development of antibodies to factor VIII (inhibitors), inevitable exposure to hepatitis, AIDS and other blood-borne viral infections, and incremental in-

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This study was supported by the Korean Academy of Medical Science Research Fund (1987).

sults to the immune system (Rizetto et al., 1982; Pollack et al., 1985).

There are three comprehensive care centers for hemophiliacs in Korea (Kim et al., 1988). These centers are located at Yonsei University Severance Hospital (Seoul), Inje University Pusan Paik Hospital (Pusan), and Chunnam University Hospital (Kwangju). Newly diagnosed or suspected patients encountered at other hospitals are referred these centers for confirmation and treatment.

The present study is the fourth report of the statistical surveys of hemophilia based on materials obtained from sixteen medical centers in Korea (Hong et al., 1964; Hong et al., 1973; Lee et al., 1976).

We reviewed and analyzed 498 cases of hemophilia which were reported by the sixteen medical centers.

MATERIALS AND METHODS

In March 1987, we sent questionnaires on hemophilia to all the University hospitals and general hospitals in the country. Reports from 13 University hospitals and 3 general hospitals contained informations regarding 498 cases of confirmed hemophiliacs. Comprehensive clinical and statistical analysis on this clinical information was done (Table 1).

The patients who were reported by several different hospitals were identified to integrate all the information and counted as a single case for each patient.

Table 1. List of Hospitals and the Number of Cases

Name of Hospital	Hemophilia A	Hemophilia B	Total
Yonsei University H.	185	28	213
S.N.U.H.	56	12	68
Inje University (Pusan)	40	6	46
Seoul Red Cross Hospital	39	0	39
Kyungpook N.U.H.	26	7	33
Jeonju Presbyterian H.	13	5	18
National Medical Center	12	4	16
Chunnam U.H.	10	2	12
Koshin U.H.	6	5	11
Kyunghee U.H.	9	1	10
Pusan U.H.	7	2	9
Wonju U.H.	6	1	7
Kemyung U.H.	6	0	6
Chunbuk U.H.	6	0	6
Chungnam U.H.	3	0	3
Chosun U.H.	1	0	1
Total (%)	425(85.3)	73 (14.7)	498(100.0)

S.N.U.H.: Seoul National University Hospital

RESULTS

1. Type and age distribution of hemophilia

The final reports on hemophilia contained a total of 498 cases of hemophiliacs, of which hemophilia

Table 2. Age Distribution of Korean Hemophilia Ptients

Age (year)	Hemophilia A	Hemophilia B	Total (%)
0- 5	81	20	101 (20.3)
6-10	114	20	134 (26.9)
11-15	86	13	99 (19.9)
16-20	72	5	77 (15.5)
21-25	21	3	24 (6.2)
26-30	14	4	18 (4.4)
>30	21	4	25 (6.8)
Total (%)	425(85.3)	73 (14.7)	498 (100.0)

Table 3. Family History of Hemophilia (n=498)

Family History	Hemophilia A	Hemophilia B	Total (%)
Negative	243	41	284 (57.0)
Positive	182	32	214 (43.0)
Brother	71	21	92 (43.0)
Maternal cousin	70	13	83 (38.8)
Maternal uncle	67	8	75 (35.0)
Maternal grandfather	7	2	9 (4.7)

*Some hemophiliacs have the positive family history more than two.

Table 4. Symptoms of Hemophilia (n=498)

Symptoms \ Age (years)	<1	1-10	11-20	>20	Total	(%)
Hemorrhagic Symptoms						
Easy brusing	26	159	128	69	382	(76.7)
Prolonged bleeding after trauma	19	129	104	45	297	(59.6)
Soft tissue hematoma	16	94	81	41	232	(46.6)
Epistaxis	6	55	74	33	168	(33.7)
Hematuria	2	15	26	28	71	(14.3)
Melena	0	15	18	18	51	(10.2)
Bleeding after teeth extraction	0	18	26	7	51	(10.2)
Bleeding after circumcision	0	6	4	2	12	(2.4)
Conjunctival hemorrhage	0	2	7	1	10	(2.0)
Hemoptysis	0	0	2	1	3	(0.6)
Joint symptoms	4	173	159	68	404	(81.1)

Table 5. Onset of Hemorrhagic Manifestations

Severity \ Age (months)	<6	6-12	13-24	25-36	37-48	>48	Total
Severe	152 (55.7)	84 (30.8)	15 (5.5)	12 (4.4)	10 (3.7)	0 (0.0)	273 (100.0)
Moderate	50 (27.5)	52 (28.6)	34 (18.7)	19 (10.4)	6 (3.3)	21 (11.5)	182 (100.0)
Mild	4 (9.3)	4 (11.6)	6 (14.0)	5 (11.6)	2 (4.7)	21 (48.8)	43 (100.0)
Total (%)	206 (41.4)	141 (28.3)	55 (11.1)	36 (7.2)	18 (3.6)	42 (8.4)	498 (100.0)

Table 6. Age at Diagnosis by Severity in Hemophilia

Severity \ Age (years)	<1	1-3	4-6	7-9	>9	Total(%)
Severe	148 (54.2)	66 (24.2)	25 (9.2)	11 (4.0)	23 (8.4)	273 (100.0)
Moderate	50 (27.5)	71 (39.0)	22 (12.1)	10 (5.5)	29 (15.9)	182 (100.0)
Mild	6 (14.0)	8 (18.6)	8 (18.6)	5 (11.6)	16 (37.2)	43 (100.0)
Total (%)	204 (41.0)	145 (29.1)	55 (11.1)	26 (5.2)	68 (13.6)	498 (100.0)

Table 7. Activated Partial Thromboplastin Time (APTT) in Hemophilia

APTT(sec)*	Hemophilia A	Hemophilia B	Total (%)
40- 60	72	18	90 (18.1)
61- 80	125	22	147 (29.5)
81-100	135	22	157 (31.5)
>100	93	11	104 (20.9)
Total	425	73	498 (100.0)

*Control 25-40 sec

Table 8. Clinical Severity of Hemophilia

	Hemophilia A (%)	Hemophilia B (%)	Total (%)
Severe	244 (57.4)	29 (39.7)	273 (54.8)
Moderate	149 (35.1)	33 (45.2)	182 (36.5)
Mild	32 (7.5)	11 (15.1)	43 (8.7)
Total (%)	425 (100.0)	73 (100.0)	498 (100.0)

A patients were 85.3% (425 cases), and hemophilia B were 14.7% (73 cases), with a ratio of 5.5: 1. The pediatric age group of patients under 15 years of age included 334 cases, 67.1% of the total (Table 2).

2. Sex

Only one of the 498 cases was female.

3. Family background

A complete pedigree of the patients revealed a familial history of hemophilia in 214 cases (43.0%), in

Table 9. Relation between Chronic Arthropathy and Severity

Chronic Arthropathy \ Severity	Severe No. (%)	Moderate No. (%)	Mild No. (%)	Total (%)
Present	163 (60.6)	68 (38.6)	5 (16.1)	236 (49.6)
Absent	106 (39.4)	108 (61.4)	26 (83.9)	240 (50.4)
Total	269 (100.0)	176 (100.0)	31 (100.0)	476 (100.0)

Table 10. Relation between Chronic Arthropathy and Age

Chronic Arthropathy \ Age (years)	< 5	5-10	11-15	16-20	>20	Total (%)
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Present	3 (3.0)	43 (32.1)	63 (63.6)	65 (86.7)	62 (92.5)	236 (49.6)
Absent	98 (97.0)	91 (67.9)	36 (36.4)	10 (13.3)	5 (7.5)	240 (50.4)
Total (%)	101 (100.0)	134 (100.0)	99 (100.0)	75 (100.0)	67 (100.0)	476 (100.0)

Table 11. Joint Involvement of Chronic Arthropathy in Hemophilia (n=236)

Site	No. of Patients (%)
Knee	210 (89.0)
Elbow	53 (22.5)
Ankle	51 (21.5)
Hip	29 (12.3)
Wrist	5 (2.1)
Shoulder	2 (0.8)

Table 12. Management of Arthropathy in Hemophilia

Type of Arthropathy	Management	No. of Patients (%)
Acute arthropathy (n=388)	Replacement therapy	323 (83.2)
	Conservative care*	307 (79.1)
	Splint	143 (36.9)
	Physiotherapy & muscle training	99 (25.5)
	Joint aspiration	7 (1.8)
	Surgery	2 (0.5)
Chronic arthropathy (n=236)	Rehabilitation	60 (25.4)
	Home exercise	107 (45.3)
	Orthopedic appliance	48 (20.3)
	Surgery	7 (3.0)
	No treatment	120 (50.8)

*Conservative care: ice bag application & elastic bandage compress

order of siblings (43.0%), maternal cousins (38.8%), maternal uncles (35.0), and maternal grandfathers (4.7%). Some hemophiliacs have more than two family history (Table 3).

4. Symptoms in different age groups

The most common symptoms presented at admission were bleeding tendency (76.7%) and joint symptoms, followed by post-traumatic bleeding (59.6%), and hematuria (46.6%). The joint symptoms were prevalent in the physically active age group from 1 year through 20 years of age (Table 4).

5. Relationship between hemorrhagic symptoms and the severity of the disease

The patients who exhibited hemorrhagic symptoms before 1 year of age numbered 347 cases (69.7%), suggesting that the majority of the patients presented early manifestations. In relation to the severity of the disease, hemorrhagic symptoms were observed before 1 year of age in 86.5% of 273 patients with severe hemophilia (Table 5).

6. Relationship between the age at initial diagnosis and severity of the disease

Table 13. Complications of Hemophilia

Complication	Hemophilia A	Hemophilia B	Total (%)
Intracranial hemorrhage	40*	8	48 (45.3)
Gastrointestinal bleeding	23	1	24 (22.6)
Nerve Palsy	11**	2	13 (12.3)
Hemoperitoneum	11	1	12 (11.3)
Hemothorax	4	2	6 (5.7)
Sepsis	3	0	3 (2.8)
Total	79	14	106 (100.0)

* 3 cases expired due to ICH

** Nerve palsy: Femoral nerve involvement in 7 cases. Ulnar nerve involvement in 3 cases. Median nerve involvement in 2 cases.

Table 14. Number of Visits to Hemophilia Clinic or E R by Hemophilia Patients (n=213)

Number of visits (/year)	No. of Patients (%)
≤10	18 (8.5)
11-15	39 (18.3)
16-20	59 (27.7)
21-25	84 (39.4)
26-30	5 (2.3)
>30	8 (3.8)

E R : Emergency room

Table 15. Amounts of Replacement Therapy Received by hemophilia A Patients (n=182)

Factor VIII administered (U/kg/year)	No. of Patients (%)
≤ 200	21 (11.5)
201 - 400	32 (17.6)
401 - 600	34 (18.7)
601 - 800	48 (26.4)
801 -1,000	22 (12.1)
> 1,000	25 (13.7)

Table 16. Average Costs of Replacement Therapy for Hemophilia Patients (n=182)

Average costs (10^4 Won/year)	No. of patients (%)
≤ 100	15 (8.2)
101- 300	28 (15.4)
301- 500	40 (22.0)
501- 700	52 (28.6)
701-1,000	35 (19.2)
> 1,000	12 (6.6)

In the severe cases, with the factor VIII or IX level less than 1% by quantitative analysis more than half (54.2%) were diagnosed before 1 year of age, while in the moderate cases, 27.5%, and in the mild cases, 14.0%, suggesting that the more severe the disease, the earlier the diagnosis due to early manifestation of hemorrhagic symptoms (Table 6).

7. Activated partial thromboplastin time (APTT)

In all of the patients (498 cases), the APPT was prolonged, i.e. over 40 seconds, and 261 cases showed severe prolongation of the APTT over 80 seconds (Table 7).

8. Distribution of the disease severity

The severe cases (factor VIII or IX level less than 1%) were observed in 273 patients (54.8%), the moderate (factor VIII or IX level of 2-5%) in 182 (36.5%), and the mild cases (factor VIII or IX level of 6-25%) in 43 (8.7%). (Table 8).

9. Chronic hemophilic arthropathy

Chronic arthropathy was found in 236 (49.6%) of the 476 cases which were evaluated for it. In the severe hemophiliacs, 60.6% suffered chronic arthropathy, while in the mild cases, 16.1% (Table 9). In addition, in the age groups 11-15 years, 16-20 years, and over 20 years, respectively, 63.6%, 86.7%, and 92.5% of the patients had chronic arthropathy. This observation revealed that the prevalence of chronic arthropathy increased as the age increased (Table 10).

10. Sites of the chronic arthropathy

The joints involved most frequently were knees (89.0%), followed by elbows (22.5%), and ankles (21.5%) (Table 11).

11. Therapeutic aspect of arthropathy

For acute hemarthrosis, more than 80% of 388 cases reviewed had factor replacement therapy and conservative care. On the other hand, for chronic arthropathy, only 25.4% received rehabilitation and

Table 17. Hepatitis Markers in Hemophilia (n=122)

Hepatitis marker	Positive		Negative		Total
	No.	%	No.	%	
HBs Ag	9	7.4	113	92.6	122
Anti-HBs	100*	82.0	22	18.0	122
Anti-HBc	11	21.6	40	78.4	51

*Hepatitis vaccination was given to 23 patients.

Table 18. Antibodies to H I V in Hemophilia A and B

	Total	Positive	
	No.	No.	%
Hemophilia A	110	1	0.9
Hemophilia B	12	1	8.3
Total	122	2*	1.6

HIV: Human immunodeficiency virus
* 2 patients were confirmed by Western blot assay.

13. Frequency of visits to the OPD and Emergency Room

The average frequency of visits to the hospital for 213 patients registered at the Hemophilia Clinic of the Severance Hospital during the year 1987 was 16 times/year in 156 cases (73.2%). In other words, most of the patients visited the hospital more than once a month (Table 14).

14. Yearly total amounts of facotr VIII replacement therapy

Of the 182 hemophilia A patients who visited the Hemophilia Clinic more than once, the majority (over 50%) received over 600 U/Kg factor VIII concentrates per year (Table 15).

15. Yearly average costs for replacement therapy

More than half (55.4%) of 182 hemophilia A patients paid over 5 million won in one year for their treatment (Table 16).

Table 19. T Lymphocyte Subpopulations in Patients and Controls

Subjects	Percentage of cells staining			T4/T8 Ratio
	T cells	T helper (T4)	T suppressor (T8)	
Patients (n=50)				
HIV (−) (n×48)	68.5±9.7*	41.1±10.1**	33.4±8.3**	1.33±0.53**
HIV (+) (n= 2)	77	33	51.5	0.64
Controls (n=20)	74.4±7.9	50.1±7.9	21.8±4.6	2.27±0.48

Results expressed as mean±SD.
* $P<0.05$ by Wilcoxon rank sum test when compared to control.
** $P<0.001$ when compared to control.

Table 20. In Vitro Lymphocyte Functions in Patients and Controls

	Phytohemagglutinin (cpm)	Concanavalin A (cpm)	Natural killer (% cytotoxicity)
Patients (n=50)	44,250±26,732*	40,323±32,975*	37.3±18.6**
Controls (n=20)	62,045±19,108	54,884±21,171	51.5±11.9

Results expressed as mean±SD.
* $p < 0.05$ when compared to control.
** $p < 0.001$ when compared to control.

50.8% neglected any forms of therapy resulting in disability in daily living activities (Table 12).

12. Complications

The most common hemorrhagic complication was intracranial hemorrhage, which occurred 48 cases (45.3%) of whom 3 died. The others were GI bleeding in 24 cases (22.6%), and peripheral nerve palsy in 13 cases (12.3%) (Table 13).

DISCUSSION

Hemophilia was reported by Rabbi Simon Ben Gaiel in the Talmud in the second century A.D., long before its first description in medical literature by Otto in 1803 (Hilgartner and Mcmillan, 1984) The incidence of hemophilia cannot be stated with accuracy at this

time because registration of all patients with mild and severe disease is incomplete in most countries. Biggs (1977) reported that its incidence at birth in the United Kingdom is approximately 7 per 100,000 males. In Korea, its incidence at birth is not clear, but 498 cases of hemophilia were enrolled in three hemophilia comprehensive care centers. Hemophilia A comprised 425 cases (85.3%) and the remaining 73 cases (14.7%) were hemophilia B. The hemophilia A to B ratio is approximately 5.5:1. Because of the high mutation rate for hemophilia (Barrai et al., 1968), as many as one-third of hemophilic patients have no affected family members that can be discovered either by careful history review or reconstruction of the family tree, suggesting that about 15 to 20% of all cases are sporadic, although application of more modern carrier-testing techniques may well reduce these statistics. A previous study done by Nilsson et al. (1961) revealed that the positive family history was 75-85%. In this survey, the family background for hemophilia was positive in 43.0%. Hemarthrosis is the most characteristic lesion of hemophilia and the most commonest cause of morbidity, occurring in 90% of severely affected patient. Chronic destructive arthropathy develops in 60% of patients with severe hemophilia (Jadle, 1987), but this study showed that 49.6% of 498 hemophiliacs developed chronic arthropathy and the incidence increased significantly with age. The joints most frequently affected were the knee (89.0%), the elbow (22.5%), and ankles (21.5%). Chronic hemophilic arthropathy can improve remarkably from several weeks or months of intensive physical therapy for muscle building and increased joint stability, avoiding bearing weight, and regular prophylactic infusion of factor VIII or factor IX to prevent traumatic bleeding. The most commonly employed management of chronic arthropathy was rehabilitation in 25.4% of cases, but in 50.8% neither physical therapy or muscle stretching exercise were given. Thus, most of the patients with chronic arthropathy had trouble in performing daily activities. The major complication in this survey was intracranial hemorrhage in 48 cases (45.3%). The reported incidence of CNS bleeding in hemophiliacs was ranged from 2.2% to 7.8% (Pito-Tenanos et al., 1983). In one cooperative study of 2,500 hemophiliacs studied over 10 years, 71 episodes of central nervous system bleeding were documented. There was a mortality rate of 34%, and 47% of the survivors were left with mental retardation, seizure disorders, or motor impairment (Eyster et al., 1978). Prior to the use of factor concentrates, the mortality after intracranial hemorrhage was greater than 70%. This is now decreased to approximately 25% in most centers (Martinowitz et al., 1986).

For the control of bleeding in hemophiliacs, repeated infusions of plasma products containing clotting factors VIII and IX are required. There is an increasing number of reports that repeated infusions of plasma products may be associated with transfusion mediated viral disease as well as AIDS, and impairment of cellular immunity. Previous reports have demonstrated impairment of cell-mediated immunity in asymptomatic hemophiliacs treated with lyophilized factor VIII concentrates (Landay et al., 1983; Carr et al., 1984; Goldswith et al., 1985; Lee et al., 1985).

In 1987, two hemophiliac boys (one hemophilia A and the other hemophilia B) became positive for Human immunodeficiency virus (HIV) antibodies. These are also the first cases of seroconversion in Korean hemophiliacs.

Kim and Yang (1988) evaluated the cell mediated immunity in Korean asymptomatic hemophiliacs who received commercially prepared lyophilized concentrates uncontaminated by HIV. As a result, (1) HBs Ag was positive in 9 (7.4%) out of 122 cases and anti-HBs was positive in 100 cases (82%) (Table 17). (2) Antibodies to HIV were detected in 2 (1.6%) of 122 hemophiliacs patients (Table 18). (3) Low helper T/suppressor T cell ratios and high total T8 counts, low in vitro Phytohemagglutinin (PHA) and Concanavalin A (Con A) stimulation with decreased Natural killer (NK) cell activity were observed in hemophilic patients (Table 19, 20). (4) The hemophilia patients showed a lower production of Interleukin II (IL-II) compared to healthy controls. In 23 hemophilia patients IL-II was undetected.

The hemophilic population is a group that has received a great deal of attention with respect to the HIV. Heat treatment of clotting factor concentrate was not widely applied in world until 1984. It has been suggested that hemophiliacs treated with heat-treated factor VIII concentrate rarely develop HIV seropositivity (Felding, 1985; Rouzioux et al., 1985; van der Meer et al., 1986; Klm et al., 1987). In our country, heat treated factor VIII and IX concentrates, produced by the Hyland Co. (USA) have been recently used for treatment since April 1987 in Severance hospital.

There have been considerable changes in treatment, such as the widespread availability of home therapy. Since the early 1970's, the concept of "home care" for hemophilia has steadily gained in popularity and acceptance in the United States.

The concentrate has made early and intensive home therapy possible, resulting in decreased time lost from work and school for the parent and child respectively, and thus overall costs of health care have

greatly declined for patients treated with these materials (Smith and Levine, 1984).

The economic impact of doubling or tripling the yield of factor VIII concentrates can be enormous. The major disadvantage is cost. The financial cost of hemophila, estimated to be in the range of 3 to 10 million won yearly per patient must be addressed. The many ramifications of this life long expensive and crippling illness must be considered, or the efficacy of treatment will be impaired ant the outcome will be poor. Hemophilia societies are a useful sourse of paramedical support and information. Severance Hospital opened a comprehensive care center for hemophiliacs in February 1987.

Despite these advances, however, many problems remain. Hemophilia is a multifaced disorder that can potentially affect many organ systems. Therefore, a team approach to comprehensive care for hemophiliacs is necessary. The team should be include, in addition to hematologists, orthopedic surgeons, a physical therapist, medical social workers, a dentist, physiatrists of rehabilitation, a genetic counselor, and phychologists.

REFERENCES

Barrai I, Conn HM, Cavalli-forza LL, de Nicola P: *The effect of parental age on rates of mutation for hemophilia and evidence for differing mutation rates for hemophilia A and B. Am J Hum Genet 20:175-196, 1968.*

Biggs R: *Haemophilia treatment in the United Kingdom from 1969 to 1974. Br J Haematol 35:487-504, 1977.*

Carr R, Edmund E, Prescott RJ, Veitch SE, Peutherei JF, Steel CM, Ludlam CA: *Abnormalities of circulating lymphocyte subsets in hemophiliacs in an AIDS-free population. Lancet 11;1431-1434, 1984.*

Eyster ME, Gill FM, Blatt PM: *Central nervous system bleeding in hemophiliacs. Blood 51:1179-1188, 1978.*

Felding P: *Absence of antibodies to LAV/HTLV-III in haemophiliacs treated with heat-treated factor VIII concentrate of American origin. Lancet 2:832-833, 1985.*

Goldsmith JM, Kalish SB, Green D, Chniel JS, Wallemark C, Phair JP: *Sequential clinical and immunologic abnormalities in hemophiliacs. Arch Intern Med 145:431-434, 1985.*

Hilgartner MW, McMillan CW: *Coagulation disorders. In Miller DR, Bahner RL, McMillan CW: Blood disease of Infancy and Childhood. 5th ed. St. Louis, CV Mosby Co., p 867, 1984.*

Hong CE et al: *Statistical studies on hemophilia in Korea. Kor J Hematol 3;17-21, 1964.*

Martinowitz U, Heim M, Tadmor R, Eldor A, Rider I, Findler G, Sahar A, Ramot B: *Intracranial hemorrhage in patients with hemophilia. Neurosurgery 18:538-541, 1986.*

Nathan DG, Oski FA: *Hematogy of infancy and childhood. 3rd ed. Philadelphia, WB Saunders Co., p. 305, 1987.*

Nilsson IM, Blamback M, Ramgren O: *Hemophilia in Sweden. Acta Med Scand 170:665-682, 1961.*

Pito-Tezanos M, Fernandez J, Zirulnik J, Perez-Bianco R: *Central nervous system hemorrhage in hemophilic patient : Analysis of 101 episodes. Presented at the XVth World Federation of Hemophilia Congress, Stockholm, Sweden, Jun 1983.*

Pollack S, Atias D, Yoffe G, Katz R, Shechter Y, Tatarsky I: *Impaired immune function in hemophilia patients treated exclusively with cryoprecipitate : Relation to duration of treatment. Am J Hematol 20:1-6, 1985.*

Rizetto M, Morello C, Mannucci PM, Gocke DJ, Spero JA, Lewis JH, Van Thiel DH, Scaronic F: *Delta infection and liver disease in hemophilic carriers of hepatitis B surface antigen. J Infect Dis 145:18-22, 1982.*

Rouzioux C, Chamaret S, Montagnier L: *Absence of antibodies to AIDS virus in haemophiliacs treated with heat-treated factor VIII concentrates. Lancet 2:271-272, 1985.*

Spero JA, Lewis JH, Van Thiel DH, Hasiba U, Rabin BS: *Asymptomtic structural liver disease in hemophilia. N Engl J Med 298:1373-1378, 1978.*

Smith PS, Levine PH: *The benefits of comprehensive care of hemophilia: A five year study of outcome. Am J Public Health 74:616-617, 1984.*

Van der Meer J, Daenen S, Van Imhoff GW, de Wolf JTM, Hallie MR: *Absence of seroconversion for HTLV-III is hemophiliacs intensively treated with heat treated factor VIII concentrate. Br Med J 292:1049, 1986.*

Hong CE et al: *Statistical studies on hemophilia in Korea. Kor J Hematol 8:67-73, 1973.*

Jandl JH: *Blood: Textbook of hematology, 1st ed. Boston, Little Brown Co., p 1095-1140, 1987.*

Kim KY et al: *Statistical studies on hemophilia in Korea. Kor J Hematol 23:255-265, 1988.*

Kim KY, Yang CH: *A study of HBs markers, HIV seropositivity and cell mediated immunity in Korean hemophiliacs, presented at the XXVth World federation of Hemophilia Congress, Madrid, Spain, May 1988.*

Kim HC, Nahum K, Raska K, Goche DJ, Kosmin M, Karp GI, Saidi P: *Natural history of acquired immunodeficiency syndrome in hemophilic patients. Am J Hematol 24:169-176, 1987.*

Landay A, Poon MC, Abo T, Stagno S, Cooper MD: *Immunologic studies in asymptomatic hemophilia patients. J Clin Invest 71:1500-1504, 1983.*

Lee CA, Janossy BG, Thomas HC, Rizza CR, Kernoff PBA: *Relationships between blood product exposure and immunological abnormalities in English haemophiliacs. Br J Haematol 60:161-172, 1985.*

Lee MH et al: *Statistical studies on hemophilia in Korea. Kor J Hematol 11:11-18, 1976.*

Mannucci PM, Ronchi G, Rota L, Colombo M: *A clinicopathological study of liver disease in haemophiliacs. J Clin Pathol 31:779-783, 1978.*