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Epidemiology of Congenital Bleeding Disorders: a Nationwide Population-based Korean Study

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ABSTRACT

Background: Except for data in the Korea Hemophilia Foundation Registry, little is known of the epidemiology of congenital bleeding disorders in Korea.
Methods: Data were obtained from the Korean Health Insurance Review and Assessment Service (HIRA) database.
Results: From 2010 to 2015, there were 2,029 patients with congenital bleeding disorders in the Korean HIRA database: 38% (n = 775) of these patients had hemophilia A (HA), 25% (n = 517) had von Willebrand disease (vWD), 7% (n = 132) had hemophilia B (HB), and 25% (n = 513) had less common factor deficiencies. The estimated age-standardized incidence rate (ASR) of HA and HB was 1.78–3.15/100,000 and 0.31–0.51/100,000, respectively. That of vWD was 1.38–1.95/100,000. The estimated ASR of HA showed increase over time though the number of new patients did not increase. Most patients with congenital bleeding disorders were younger than 19 years old (47.8%), and most were registered in Gyeonggi (22.1%) and Seoul (19.2%).
Conclusion: This is the first nationwide population-based study of congenital bleeding disorders in Korea. This study provides data that will enable more accurate estimations of patients with vWD. This information will help advance the comprehensive care of congenital bleeding disorders. We need to continue to obtain more detailed information on patients to improve the management of these diseases.

Keywords: Congenital Bleeding Disorder; Epidemiology; Korea; Nationwide

INTRODUCTION

Congenital bleeding disorders are rare diseases caused by deficiencies of protein cofactors and enzymes involved in blood coagulation.[1,2] The most common coagulopathies are von Willebrand disease (vWD), an autosomal inherited bleeding disorder caused by a deficiency or abnormality of von Willebrand factor; hemophilia A (HA); and hemophilia B (HB). HA and HB are X-linked inherited disorders caused by deficiencies of factors VIII and IX, respectively.[1]

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Disclosure
The authors have no potential conflicts of interest to disclose.

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The Korea Hemophilia Foundation (KHF) publishes an annual report on its patient registry, including patient demographics and data on the utilization of health services.[3] However, patients who are not enrolled in the KHF are not properly identified. Some patients are reluctant to register in the KHF for various reasons. Others may not be diagnosed properly. Therefore, it is difficult to accurately ascertain the number of people with congenital bleeding disorders in Korea. According to the 2018 KHF Annual Report, there were 2,458 registered patients, including 1,889 (77%) with HA, 450 (18%) with HB, and only 136 (5%) with vWD.[3] According to the 2018 annual global survey of the World Federation of Hemophilia (WFH), there are 2,423 hemophilia patients in Korea.[4] Australia (n = 2,653) and South Africa (n = 2,332), which have similar numbers of hemophilia cases, have 2,146 and 647 vWD patients, respectively. Therefore, some congenital bleeding disorders in Korea might be underestimated.

The epidemiology of congenital bleeding disorders in Korea has not been examined using nationwide population-based data. Therefore, we examined the nationwide incidence of congenital bleeding disorders using the Korean Health Insurance Review and Assessment Service (HIRA) databases.

METHODS

Data source

The National Health Insurance (NHI) is the only public medical insurance system operated by the Ministry for Health, Welfare and Family Affairs in Korea.[5,6] The Korean NHI program covers the entire Korean population as a compulsory social insurance system. The HIRA is a government-affiliated organization created to build an accurate claims review and quality assessment system for the NHI.[7] The HIRA database is a "fee-for-service" system. Disease codes used in the database are standardized according to the Korean Classification of Disease, which follows the International Classification of Disease, 10th edition. HIRA databases are open for all investigators with academic purposes. Because the Korean population itself is fairly ethnically homogenous, both the NHI and HIRA databases can be readily used for nationwide analyses. For this study, we utilized information from the HIRA and NHI databases between January 2010 and December 2015. We also used the National Health Insurance Service National Sample Cohort (NHIS-NSC) data for analyzing of population according to residence distribution.

Study population

The study population consisted of patients with congenital bleeding disorders of all ages. Patients coded as having a diagnosis of congenital bleeding disorder (D660, D670, D680, D681, and D682) from January 2010 to December 2015 were selected. We excluded patients initially diagnosed as having congenital bleeding disorders from January 1, 2005 to December 31, 2009. The reason for excluding patients in this period is that the patients diagnosed before 2010 may have been counted as new patients in 2010. This identified 2,029 patients diagnosed with congenital bleeding disorders between 2010 and 2015.

Statistical analyses

The overall incidence was calculated as the number of patients diagnosed with a congenital bleeding disorder divided by the total number medical beneficiaries in 2010–2015. According to NHI data, the population of Korea was 48,887,027 in 2010 and 51,529,338 in 2015.[8] Age-standardized incidence rate (ASR) is defined as weighted average incidence rate of age-

specific rate. The standard population for ASR in our study was obtained from population of the middle of the year (2010–2015) in the Statistics Korea. Ages were grouped as follows: 0–4, 5–9, 10–14, 15–19, 20–24, 70–74, 75–79, 80–84, and ≥ 85 years of age. Descriptive analyses were used to compare children (aged < 19 years) and adults (aged ≥ 19 years). Logistic regression analyses were performed to evaluate incidence rates by age and diagnosis year.

Ethics statement

This study was approved by the Institutional Review Board of the National Health Insurance Service Ilsan Hospital (NHIMC 2019–01–028). Informed consent was waived.

RESULTS

We identified 2,029 patients with congenital bleeding disorders during the 6-year period. The overall incidence of congenital bleeding disorders was 0.78/100,000 person-years. HA was the most frequent disorder with 775 patients identified, accounting for 38% of all patients included between January 2010 and December 2015 (**Fig. 1**). Although vWD has been widely known as the most common congenital bleeding disorder, only 517 patients with vWD were identified, accounting for 25% of the total number of patients in the 6 years. Patients with HB made up 7% (n = 132) of the total. Patients with factor XI deficiency accounted for 5% (n = 92) of the total. Other rare congenital bleeding disorders were deficiencies of factors I, II, V, VII, X, XII, and XIII, which affected 25% (n = 513). **Fig. 2** shows the trend in the numbers of patients registered with congenital bleeding disorders in the last 6 years. These data do not represent a gradual increase or decrease on simple number each year. However, HA had a gradual increase of the estimated ASR in HA from 2010 (1.78/100,000) to 2014 (3.15/100,000) (**Table 1**).

The estimated ASR of HA is 1.78–3.15/100,000 people per year. That for vWD was 1.38–1.95/100,000 people per year between 2010 and 2015 (**Table 1**). Highest proportion (47.8%) of patients with congenital bleeding disorders was diagnosed at age under 19 years old. For all disorders except factor XI deficiency, more than half of patients were diagnosed at < 19 years of age (**Fig. 3**). The geographic distribution of the patients with congenital bleeding disorders in Korea most in Gyeonggi (22.1%) and Seoul (19.2%) (**Table 2**). However, the estimated ASR of HA was the highest in Daejeon (5.81/100,000) and that for vWD was the highest in Daegu and Gyeongbuk, respectively (4.78/100,000 and 3.51/100,000).

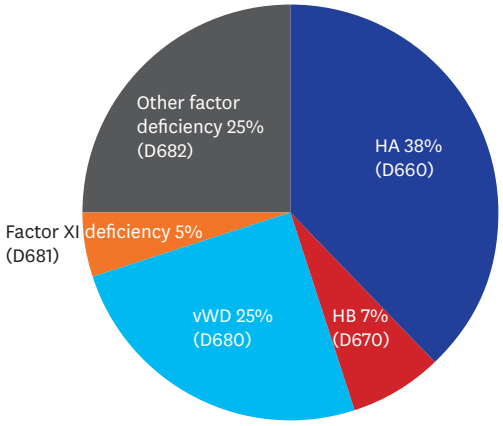

Fig. 1. Patients with congenital bleeding disorders reported in the Korean HIRA database from 2010 to 2015.
HIRA = Health Insurance Review and Assessment Service, HA = hemophilia A, HB = hemophilia B, vWD = von Willebrand disease.

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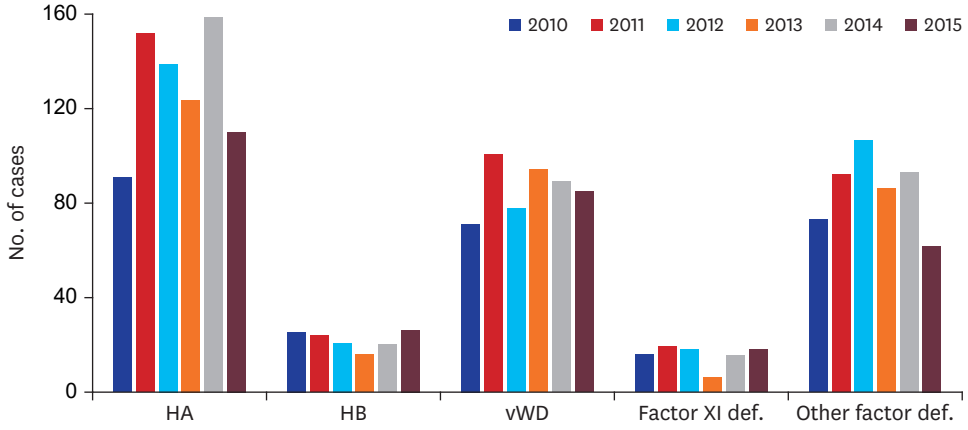

Fig. 2. Trends in the total numbers of patients with bleeding disorders registered in the Korean HIRA database from 2010 to 2015.
HIRA = Health Insurance Review and Assessment Service, HA = hemophilia A, HB = hemophilia B, vWD = von Willebrand disease.

Table 1. Age standardized incidence rate of each congenital bleeding disorder by year

Variables	Year					
	2010	2011	2012	2013	2014	2015
Diseases						
HA	91	152	139	124	159	110
HB	25	24	21	16	20	26
vWD	71	100	78	94	89	85
Factor XI def.	16	19	18	6	15	18
Others	73	92	107	86	93	62
Populations	48,887,027	49,404,648	50,114,406	50,849,278	51,234,690	51,529,338
ASR, per 100,000						
HA	1.7867	3.0083	2.7460	2.4607	3.1548	2.1903
HB	0.4999	0.4803	0.4133	0.3163	0.3942	0.5163
vWD	1.3811	1.9539	1.5367	1.8685	1.7840	1.7058
Factor XI def.	0.3204	0.3718	0.3563	0.1187	0.3041	0.3645
Others	1.4577	1.8262	2.1232	1.6955	1.8327	1.2323

HA = hemophilia A, HB = hemophilia B, vWD = von Willebrand disease, ASR = age standardized rate.

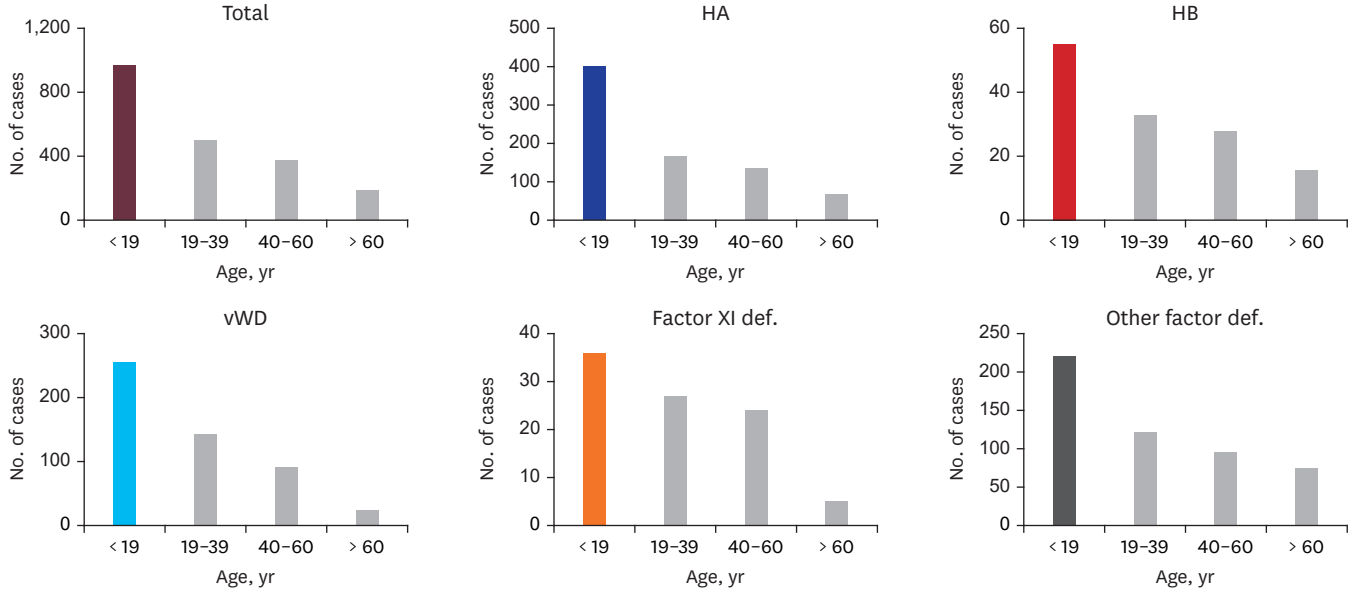

Fig. 3. Distributions of patients with congenital coagulation disorders according to age during 6 years.
HA = hemophilia A, HB = hemophilia B, vWD = von Willebrand disease.

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Table 2. Distributions of patients with congenital coagulation disorders according to region for 6 years

Region	HA	HB	vWD	Factor XI def.	Others	Total	%
Gyeonggi	166 (2.23)	35 (0.46)	101 (1.35)	30 (0.39)	117 (1.55)	449	22.1
Seoul	139 (2.37)	20 (0.34)	99 (1.67)	26 (0.43)	105 (1.82)	389	19.2
Gyeongnam	58 (2.83)	9 (0.45)	23 (1.13)	4 (0.19)	78 (3.84)	172	8.5
Gyeongbuk	36 (2.34)	6 (0.36)	52 (3.51)	5 (0.34)	35 (2.23)	134	6.6
Daegu	36 (2.50)	6 (0.40)	70 (4.78)	3 (0.19)	18 (1.25)	133	6.6
Busan	47 (2.29)	9 (0.47)	24 (1.28)	3 (0.15)	38 (1.92)	121	6.0
Daejeon	56 (5.81)	7 (0.73)	11 (1.16)	3 (0.31)	10 (1.07)	87	4.3
Chungnam	39 (3.16)	5 (0.42)	13 (1.05)	1 (0.07)	20 (1.61)	78	3.8
Incheon	36 (2.08)	10 (0.59)	12 (0.70)	6 (0.34)	13 (0.78)	77	3.8
Jeonnam	33 (3.05)	6 (0.49)	22 (2.07)	4 (0.37)	6 (0.49)	71	3.5
Jeonbuk	27 (2.46)	3 (0.30)	20 (1.78)	1 (0.08)	14 (1.25)	65	3.2
Gwangju	24 (2.61)	5 (0.54)	25 (2.73)	1 (0.12)	8 (0.88)	63	3.1
Gangwon	25 (2.78)	1 (0.11)	14 (1.65)	2 (0.23)	15 (1.69)	57	2.8
Chungbuk	11 (1.19)	5 (0.49)	14 (1.51)	1 (0.10)	20 (2.14)	51	2.5
Ulsan	13 (1.93)	1 (0.14)	6 (0.82)	0 (0)	8 (1.19)	28	1.4
Jeju	9 (2.35)	1 (0.25)	6 (1.82)	1 (0.23)	5 (1.48)	22	1.1
Sejong	3 (3.36)	0 (0)	2 (2.17)	0 (0)	0 (0)	5	0.2
Missing data	17	3	3	1	3	27	1.3
Total	775	132	517	92	513	2,029	100.0

Values are expressed as number (age standardized incidence rate).
HA = hemophilia A, HB = hemophilia B, vWD = von Willebrand disease.

DISCUSSION

A few epidemiology studies have evaluated the incidence of congenital bleeding disorders in Korea. Most have been reported by the KHF.[3,4,9,10] To the best of our knowledge, this is the first nationwide study of the entire population to analyze the incidence of congenital bleeding disorders in Korea using HIRA databases.

The most frequent bleeding disorder found in this study was HA (38%), followed by vWD (25%) and HB (7%). This result is very similar to the WFH 2018 Annual Global Survey, in which HA accounted for 51% (173,711), followed by vWD (23%; 78,547) and HB (10%; 34,289).[4] However, only 5% (135) of those in the KHF are vWD patients, contrasting studies showing that vWD is known to be one of the most common congenital bleeding disorders.[3,11-13] Given the high prevalence of vWD across ethnic groups, there were very few reported patients.[14] In Korea, 2,423 hemophilia patients were reported in 2018. South Africa and Australia, which have similar numbers of hemophilia patients, reported significantly more vWD patients, with 2,146 and 647, respectively.[4] When patients are diagnosed with congenital bleeding disorders in Korea, registration in the KHF is usually recommended. However, some patients may be reluctant for their disease to be known. Moreover, patients with mild hemophilia or vWD do not feel the need to register with the KHF for treatment because they do not need regular therapy. We found that vWD is likely to be underestimated despite the marked increase in hemophilia patients in Korea determined using nationwide data.

Patients classified as other factor deficiency accounted for a large portion (25%) in our study. Unfortunately, further detailed disease classification was not available due to many limitations in HIRA and NHIS data. A comprehensive study is necessary in order to identify the details of rare congenital bleeding disorders in Korea. Patients with factor XI deficiency accounted for 5% of the total number of patients (92/2,029) recorded for 6 years in this study. According to KHF, registered patients with factor XI deficiency was 0.9% (23/2,458) by 2018

in Korea.[3] Italian Registry of congenital bleeding disorders also reported similar proportion (0.7%, 82/11,000) in factor XI deficiency by 2015.[15]

In some countries, the annual prevalence of congenital bleeding disorders has increased in recent decades.[4,15-20] The KHF also reported that the number of registered patients had tripled. While the total Korean population increased by 12%, the KHF data showed a 200% increase in hemophilia from 997 patients in 1991 to 2,148 in 2012.[9] We also found a moderate increase of the estimated ASR in HA from 2010 (1.78/100,000) to 2014 (3.15/100,000) though significant change in the simple number of patients with HA did not show from 2010 to 2015.

After stratifying by age group, the greatest proportion of patients in the WFH 2018 Annual Report was younger than 19 years compared to other age groups.[4] According to the 2018 KHF, 645 (26.3%) of 2,458 registered patients were < 19 years.[3] In our study, the age group with the highest proportion of patients was < 19 years (47.8%), followed by ages 19–39 (24.3%) and 40–59 (18.4%) years. There may be some variation in the age distributions of patients with congenital bleeding disorders across countries. Because they are inherited disorders, they are often diagnosed at an early age. However, some are diagnosed in older patients. The life expectancies of these patients are increasing with active factor therapy, and patients with mild symptoms who are diagnosed at old age are also increasing with advances in diagnostic technology.

The most patients were registered in Gyeonggi (22.1%) and Seoul (19.2%) because these provinces have the largest populations. However, the estimated ASR of HA was the highest in Daejeon (5.81/100,000) and that for vWD was the highest in Daegu and Gyeongbuk, respectively (4.78/100,000 and 3.51/100,000). We guess that it may be affected by the institution according to region. The geographic distribution in other regions was heterogeneous.

There are some limitations to using the HIRA databases. First, the diagnoses of congenital bleeding disorders were based on codes, without laboratory results. Second, other rare congenital bleeding disorders accounting for 25% of the cases in this study, such as deficiencies in factors I, II, V, VII, X, XII, and XIII, were not analyzed separately in this study. It would be better to study these diseases separately in the future. Third, we did not analyze details about congenital bleeding disorders including the prevalence, mortality rate, viral infection due to treatment, classification according to disease severity, trends in the use of factor concentrates, or the cost of congenital bleeding disorders.

Nevertheless, our study is meaningful as it is the first nationwide population-based study of congenital bleeding disorders in Korea. This retrospective study permitted the calculation of more accurate incidences of these diseases in Korea. We also accurately assessed the number of patients with vWD, who have been poorly identified to date. Our data on the incidence of congenital bleeding disorders may give some useful systematic information. A system for collecting more detailed data on congenital bleeding disorders is needed.

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