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Occurrence Rates of Inherited Bleeding Disorders Other Than Hemophilia and von Willebrand Disease Among People Receiving Care in Specialized Treatment Centers in the United States

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To the Editor:

The United States Hemophilia Treatment Centers Network (USHTCN) is made up of 145 hemophilia treatment centers (HTCs) located throughout the United States with funding from the Health Resources and Service Administration and the Centers for Disease Control and Prevention (CDC) to facilitate monitoring of health care and outcomes among people with bleeding disorders. Inherited bleeding disorders most often treated at US HTCs are hemophilia[1,2] and von Willebrand disease (VWD);[3] however, these centers also provide care for people with a variety of other disorders, including deficiencies of coagulation factors other than factor VIII and IX, platelet disorders, fibrinolytic defects, and connective tissue disorders with an associated bleeding phenotype. Community Counts,[4] a combined effort of the USHTCN, the American Thrombosis and Hemostasis Network (ATHN), and the CDC to gather and share information about common health issues, medical complications, and causes of death of people with bleeding disorders, includes a component known as the HTC Population Profile (HTC PP), for which limited data on all persons receiving care at HTCs

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Disclosures

Connie H. Miller, J. Michael Soucie, and Amanda B. Payne designed the study, conducted the research, analyzed the data and wrote the paper. Vanessa R. Byams, Karon Abe, Magdalena Lewandowska, and Amy D. Shapiro conducted the research and wrote the paper. Connie H. Miller, J. Michael Soucie, Vanessa R. Byams, Amanda B. Payne, Karon Abe, and Amy D. Shapiro state that they have no competing interests. Magdalena Lewandowska has received honoraria from Octapharma and Genentech for speaking, Spire for leading educational activities, and participating in an advisory board for Agios. All honoraria have been donated to the Indiana Hemophilia and Thrombosis Center.

have been collected since 2012. We have recently reported numbers and characteristics of males and females with hemophilia[1,2] and VWD[3] treated at HTCs using HTC PP data. The aim of this study was to use data from the HTC PP to estimate the number of people with rare bleeding disorders other than hemophilia and VWD receiving care at HTCs in the United States.

HTC staff use standardized forms[5] to collect nine HTC PP data elements each year on all people with bleeding disorders who visit an HTC for diagnosis or care in a dataset that is compliant with the Health Insurance Portability and Accountability Act (HIPAA) and in accordance with institutional policies. All data are de-identified using a unique identification code prior to electronic transmission to CDC; participant authorization for inclusion in this public health surveillance was not required at most HTCs.

Data used in this analysis included year of birth, sex, race, Hispanic ethnicity, 3-digit zip code of residence, and primary bleeding disorder diagnosis, collected on 16,781 unique individuals reported to have a primary diagnosis in one of the following categories: 1) coagulation factor deficiency of factors I, II, V, VII, X, XI, XIII, or combined V & VIII; 2) platelet disorder including Bernard-Soulier syndrome, Glanzmann thrombasthenia, Grey platelet syndrome, Hermansky-Pudlak syndrome, hereditary thrombocytopenia, platelet release defect, storage pool disease, and unspecified hereditary platelet function disorder; 3) fibrinolytic defect including plasminogen activator inhibitor-1 (PAI-1) deficiency and alpha-2 antiplasmin deficiency, 4) Ehlers-Danlos syndrome, and 5) bleeding disorder, no laboratory diagnosis. A total of 2,092 patients, 12.5% of those reported, were in the last category defined as patients with abnormal screening tests but no specific diagnosis and were excluded from the analysis. An additional 1,732 patients from a single HTC who were diagnosed with platelet disorders were excluded because they represented 26% of the platelet disorders and 44% of the storage pool disease in the entire population and were considered an outlier. The remaining 12,957 patients who received care in 143 federally supported HTCs in the U.S. (Guam and Puerto Rico territories were excluded) during the period January 2012 through March 2021 formed the study population.

The distributions of unique patients according to disorder and demographic characteristics were used to describe the populations. The sex assigned at birth was used for seven transsexual subjects. Data were analyzed using SAS Version 9.4 (SAS Institute, Cary, NC, USA). Groups were compared using Chi-square and Fisher's exact tests, as appropriate, with significance level set at $P<0.05$.

Period prevalence of each disorder was calculated by dividing the number of unique patients with at least one visit to the HTC over the nine-year period by the estimated U.S. population in 2017 of 325,719,178[6] as an approximation of the population over the surveillance period, and 95% confidence intervals (CIs) were estimated assuming a Poisson distribution. Prevalence estimates are presented in terms of persons affected per million and are referred to as HTC-treated prevalence, because no data are available on the proportion of patients with these disorders who are seen at HTCs versus those who may be treated elsewhere. We also generated prevalence estimates and associated 95% CIs based on data reported in the United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) Annual Report

for 2019[7] and the World Federation of Hemophilia (WFH) Global Survey for 2019[8] for comparison.

Among patients treated in the USHTCN (Table 1), platelet disorders were more common (51.3%) than factor deficiencies other than FVIII or FIX (42.9%). Over 50% of platelet disorders were reported as undefined, suggesting the need for improved platelet diagnostic testing in many US HTCs. Storage pool disease was the most common platelet disorder diagnosed, making up 28.8% of platelet disorders. In the single HTC from which data were excluded, platelet disorders made up 97% of all cases contributed to the study population, and storage pool disease made up 88.3% of platelet disorders diagnosed. This may be due to use of non-standard diagnostic methods or differences in referral patterns. Details on the underlying defects causing the reported platelet disorders were not collected. Of the factor deficiencies, FVII (44.9%) and FXI (27.3%) deficiencies were the most common. Although there has been increased recognition of the bleeding manifestations in disorders of fibrinolysis and connective tissue, they were uncommon, each about 3% of the study population; however, their numbers were greater than some more easily recognized disorders, such as Glanzmann thrombasthenia and factor XIII deficiency.

The US HTC-treated prevalence (Table 1) per 1,000,000 population was 20.42 (95% CI: 19.93 – 20.92) for platelet disorders, 17.08 (95% CI: 16.63 – 17.53) for factor deficiencies, 1.07 (95% CI: 0.96 – 1.19) for fibrinolytic disorders, 1.21 (95% CI: 1.10 – 1.34) for connective tissue disorders, and 39.78 (95% CI: 39.10 – 40.47) overall. For comparison, the HTC-treated prevalence of VWD was 85 cases per 1,000,000 persons.[3] As in our VWD report,[3] these prevalence estimates represent only those who were referred to specialized care centers and who have received a diagnosis. A portion of US patients with these rare disorders remain uncounted, because they are treated outside of the USHTCN; for males with hemophilia, this proportion has been estimated at 20-33%.[1] Table 1 also provides prevalence figures based on the UKHCDO Annual Report[7] and the WFH Global Survey[8] for 2019. The US HTC-treated prevalence is higher than the WFH Global Survey for all disorders. The UK prevalence figures are higher than both in most categories, perhaps due to more complete ascertainment in the UK health care system. Because the WFH Global Survey includes data from 115 countries, there may be differences in data collection and reporting methods, ascertainment of rare disorders, and populations assessed. Population differences are to be expected, because many of these disorders are caused by rare alleles that vary in frequency among populations and may be subject to founder effect. For example, FXI deficiency is most common among those of Ashkenazi Jewish ancestry. Its prevalence will reflect the migration of that population and in the United States is three times the estimated global prevalence.[8] The prevalence of rare autosomal recessive disorders often correlates with the frequency of consanguineous/endogamous marriages within a population, which varies based on religious and cultural practices. The differences observed are important, because manufacturers may underestimate the potential market for treatment products for these orphan diseases if only WFH Global Survey data are considered.

Age ranges for patients (Table 2) were similar across diagnostic categories. Age at diagnosis was not available in this dataset. Race and ethnicity (Table 2) differed significantly among the categories ($P<0.0001$). Connective tissue disorders were reported primarily in White

non-Hispanic subjects. In all categories, Black and Asian subjects were underrepresented compared to the US population[6] (10.6 vs 14.1% and 3.4 vs 6.5%, respectively; $P<0.0001$). Disease frequency may vary by race for some disorders; however, barriers to care access also warrant further exploration.

As in our previous analysis of VWD in the USHTCN,[3] females were more frequent than males with these disorders (59.4% and 41.6%, respectively). The discrepancy was most prominent in the rarer disorders of fibrinolysis (69.2% female) and connective tissue (77.5% female) and was also present in platelet disorders (62.4% female). In factor deficiencies, the difference was less pronounced (54.0% female), perhaps reflecting a lesser effect of these disorders on menstrual bleeding, a common reason for referral of women.

Rare bleeding disorders, which arise from many different alterations in the blood clotting system, often present diagnostic and treatment challenges. The need for complex diagnostic tests and individualized treatment plans makes these patients ideal candidates for care in specialized centers where expertise is concentrated. Although the original focus of US HTCs was on hemophilia patients, today their coverage has expanded. Among all 65,761 unique diagnosed patients seen in the USHTCN during the period covered by this study, people with hemophilia made up 39.9%, an almost equal number had VWD (40.4%), and the rare disorders discussed here made up 19.7%. These data provide a basis to plan care delivery that meets the needs of patients with a diversity of disorders requiring varying therapeutic interventions and modalities.

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Data Availability Statement

The Community Counts surveillance data are available via a data visualization tool that displays de-identified data on patients with bleeding disorders who are enrolled in Community Counts in an interactive, visual format (https://www.cdc.gov/ncbddd/hemophilia/communitycounts/data-viz.html). However, due to ethical restrictions related to protecting patient confidentiality, additional individual-level data generated from the Community Counts surveillance system cannot be made publicly available.

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Table 1.

Individuals with a diagnosis treated in the U.S. Hemophilia Treatment Centers Network (USHTCN) from January 2012 through March 2021 by diagnosis, excluding hemophilia and von Willebrand disease, and prevalence per 1,000,000 population of disorders in the USHTCN, United Kingdom registry data (UKHCD0),[7] and the World Federation of Hemophilia Global Survey (WFH)[8]

Disorder	USHTCN Diagnosed Patients		Prevalence per 1,000.000 population		
	n	%	USHTCN n=12,957	UKHCDO n=6,386	WFH n=46,057
Platelet Disorders					
Undefined platelet function disorder	3336	50.2	10.24	46.63	5.01
Storage pool disease	1913	28.8	5.87	--	--
Hereditary thrombocytopenia	846	12.7	2.60	--	--
Glanzmann thrombasthenia	297	4.5	0.91	2.31	0.86
Hermansky-Pudlak syndrome	114	1.7	0.35	--	--
Bernard-Soulier syndrome	79	1.2	0.24	1.53	0.20
Platelet release defects	49	0.7	0.15	--	--
Gray platelet syndrome	18	0.3	0.06	--	--
Total	6652	100.0	20.42	50.47	6.07
Factor Deficiencies					
Factor VII	2497	44.9	7.67	26.74	2.58
Factor XI	1519	27.3	4.66	54.73	1.95
Factor V	531	9.6	1.63	3.79	0.55
Fibrinogen	368	6.6	1.13	3.74	0.70
Factor X	270	4.8	0.83	4.57	0.59
Factor XIII	244	4.4	0.75	1.20	0.36
Factor II	111	2.0	0.34	0.25	0.08
Factor V+VIII	22	0.4	0.07	0.40	0.19
Total	5562	100.0	17.08	95.42	7.00
Fibrinolytic Disorders					
PAI-1 deficiency	335	96.3	1.03	--	--
Alpha-2-antiplasmin deficiency	13	3.7	0.04	--	--
Total	348	100.0	1.07		
Connective Tissue Disorders					
Ehlers-Danlos syndrome	395	100.0	1.21	--	--
Total	395	100.0	1.21		

Table 2.

Demographic characteristics of the study population by disorder category

Characteristics	Platelet Disorders		Factor Deficiencies		Fibrinolytic Disorders		Connective Tissue Disorders		All Disorders	
	n	%	n	%	n	%	n	%	n	%
Age (years)										
Under 1	48	0.7	55	1.0	*	-	*	-	105	0.8
1 – 5	436	6.6	521	9.4	23	6.6	11	2.8	991	7.6
6-11	1012	15.2	889	16.0	47	13.5	54	13.7	2002	15.5
12-19	2137	32.1	1750	31.5	124	35.6	152	38.5	4163	32.1
20-29	993	14.9	761	13.7	46	13.2	77	19.5	1877	14.5
30-39	480	7.2	501	9.0	31	8.9	36	9.1	1048	8.1
40-49	391	5.9	305	5.5	29	8.3	38	9.6	763	5.9
50-59	416	6.3	284	5.1	10	2.9	15	3.8	725	5.6
60-69	419	6.3	253	4.5	21	6.0	10	2.5	703	5.4
70+	320	4.8	243	4.4	*	-	*	-	580	4.5
Race										
White	5274	79.3	4222	75.9	284	81.6	356	90.1	10136	78.2
Black	711	10.7	621	11.2	36	10.3	7	1.8	1375	10.6
Asian	232	3.5	201	3.6	*	-	*	-	441	3.4
Other	112	1.7	81	1.4	*	-	*	-	202	1.6
Unknown	323	4.8	437	7.9	17	4.9	26	6.6	803	6.2
Ethnicity										
Non-Hispanic	5439	81.8	4358	78.4	276	79.3	356	90.1	10429	80.5
Hispanic	1033	15.5	983	17.7	66	19.0	17	4.3	2099	16.2
Unknown	180	2.7	221	4.0	6	1.7	22	5.6	429	3.3
Sex										
Male	2501	37.6	2559	46.0	107	30.7	89	22.5	5256	40.6
Female	4151	62.4	3003	54.0	241	69.3	306	77.5	7701	59.4

*Counts of ≤5 were suppressed to protect patient confidentiality when specific demographic characteristics were given. Additional cells were suppressed to prevent derivation of these counts by subtraction