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Potential of the Community Counts registry to characterize rare bleeding disorders

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Abstract

Introduction: Rare bleeding disorders (RBDs) comprise of heterogeneous coagulation factor deficiencies and platelet disorders that are underreported worldwide.

Aim: First report on RBD data from United States haemophilia treatment center network (USHTCN).

Methods: A national surveillance system for the federally recognized USHTCN developed in collaboration with the Centers for Disease Control and Prevention (CDC) and American Thrombosis and Haemostasis Network (ATHN) was queried for patients with RBDs. Patient counts were extracted from the HTC Population Profile (HTC PP) component including limited data on patients followed through the USHTCN, and from the Registry component, including patient authorized, detailed clinical data. The prevalence of RBDs in the United States was estimated based on the HTC PP data and compared to the expected national prevalence based on data extrapolated from Orphanet, an international registry.

Results: Based on the estimated prevalence of RBD in the overall 2017 US population, the cases in the HTC network were lower than expected for FI, FII, FX, and FV + FVIII deficiencies by 36%, 61%, 75% and 94%, respectively, and higher than expected for FXIII, FV, FVII, and FXI deficiencies by 7%, 14%, 33% and 185%, respectively. The proportion of RBD patients reported in the HTC PP, enrolled in the Registry, was 10.8%.

Conclusions: There is a clear need to identify individuals with RBDs who could benefit from the comprehensive care provided in the USHTCN. In addition, increased enrolment of people with

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DISCLOSURES

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all RBDs in the Registry is needed to improve knowledge of treatment outcomes of patients with RBDs in the United States.

Keywords

community counts; population profile; rare bleeding disorders; registry; surveillance

1 | INTRODUCTION

Rare bleeding disorders (RBDs) are a heterogeneous group of inherited quantitative or qualitative deficiencies of coagulation factors including Factor (F) I, prothrombin (FII), FV, FVII, FX, FXI, FXIII and combined factor deficiencies such as FV + FVIII or FII, FVII, FIX and FX (vitamin K-dependent coagulation factors deficiency [VKCFD]).[1] These disorders represent 3%-5% of all inherited coagulation factor deficiencies.[2] The majority of RBDs are autosomal recessive disorders except some forms of FXI deficiency and dysfibrinogenemias, which can be autosomal dominant or variable. Genetic alterations causing RBDs may be homozygous or compound heterozygous.[3] The prevalence of RBDs ranges from 1:300 000 for FVII deficiency to 1:2-3 million for FII and FXIII deficiency and is more common in populations with endogamous or consanguineous practices.[4] Migration of populations from African and Middle Eastern countries with higher rates of consanguinity has increased the numbers of patients with RBD in multi-ethnic Western countries.[3]

Due to the low prevalence of RBDs and the lack of quality assured, systematically collected data, evidence-based guidelines for the diagnosis and management of these disorders are inadequate.[5] Several national and international registries (eg France: www.francecoag.org; Switzerland: www.aekreg.ch; England: UKHCDO, www.ukhcdo.org; Italy, http://www.aiceonline.it/); international registries (www.rbdd.org) and creation of international registries on single deficiencies (eg FXIII; FXI: http://www.factorxi.org) have improved the epidemiologic understanding of RBDs; most notably the European Network of Rare Bleeding Disorders (EN-RBD).[2,6] Despite registry-informed advances in the understanding of RBDs, additional data are needed to validate a bleeding risk-assessment model that accounts for potential modifiers of disease and that elucidates the association between coagulation activity level and clinical bleeding severity. There is an international need for a prospective RBD registry with harmonized data collection. The United States includes an important population of RBD patients due to its size and heterogeneity. Systematic data collection on the US RBD population has been challenging for a variety of reasons, including the lack of a national concerted effort and the absence of an optimal national database capable of collecting such data.

To address this deficit, the US Haemophilia Treatment Center Network (USHTCN) collaborated with the American Thrombosis & Haemostasis Network (ATHN) and Centers for Disease Control and Prevention (CDC) to apply an established public health surveillance infrastructure developed for more common bleeding and clotting disorders to collect harmonized data on RBDs. This multiagency partnership leveraged its Community Counts initiative, which is focused on systematically collecting pertinent bleeding disorders' outcomes and complications data.[7] Community Counts is comprised of three components;

the HTC Population Profile (HTC PP), the Registry for Bleeding Disorders Surveillance (Registry) and Mortality Reporting (see Figure 1). The HTC PP, a HIPAA compliant limited data set completed on all patients, is comprised of 12 data items, including age, sex, ethnicity, race, year of birth, 3-digit zip code, insurance status, diagnosis, history of hepatitis C (HCV) or human immunodeficiency virus (HIV) infection, and the year of the visit at which information was collected. The HTC PP thus describes the population size and basic characteristics of the patients receiving care within the USHTCN. The more detailed Registry, completed on patients who approve or give informed consent, includes annual data on bleeding events, joint procedures, inhibitor development, treatment products and regimens, functional impairment and other core data elements.[7,8]

To evaluate US RBD data collection efforts and improve our understanding of these disorders, we analysed data from both the HTC PP and Registry. In addition, reported prevalence rates for each disorder available through Orphanet, an international registry for rare disorders, were utilized to estimate the potential affected US population. This potential population was compared to that reported within the HTC PP to estimate the percentage of the US RBD population followed within the HTC network. This analysis was performed to evaluate current deficits in data collection and to facilitate addressing gaps in knowledge and delivery of healthcare services.

2 | METHODS

The data reported in this manuscript were collected through collaboration of ATHN, CDC, and the Haemophilia Treatment Center Network (HTCN) using ATHN Study Manager.

Patient counts from 2012 to 2017 were extracted from the HTC PP and Registry for patients with rare coagulation factor deficiencies, including Factor (F) I, prothrombin (FII), FV, FVII, FX, FXI, FXIII, combined FV + FVIII, Alpha 2 -Antiplasmin and Plasminogen activator inhibitor-1 (PAI-1). Unspecified bleeding conditions including ‘blood coagulation disorder with prolonged coagulation time’, ‘blood coagulation disorder with prolonged bleeding time’ and ‘blood coagulation disorder with impaired clot retraction time’ were excluded from analysis. Due to inconsistent standard diagnostic definitions and laboratory assays, platelet function defects (PFD), including storage pool disorders and hereditary PFDs, were also excluded from the analyses as were patients with multiple bleeding disorders other than combined FV + FVIII deficiency.

The number of people in the United States predicted to have each RBD was estimated using the disease-specific prevalences reported on Orphanet applied to the total US population in 2017. Orphanet was established in 1997 in France to gather epidemiologic and clinical data on rare disorders to improve diagnosis and treatment. A network of 37 countries, located primarily in Europe, contribute data to the system. Using the estimates of the expected number of RBD patients in the US generated from Orphanet data extrapolation, we calculated the proportion of US RBD patients represented in the HTC PP. Similarly, we calculated the proportion of RBD patients in the HTC PP who were also included in the Registry to gauge the representativeness of the Registry data.

The EN-RBD was established in March 2007 by thirteen European treatment centres from eleven countries. The aim of the EN-RBD project is to bridge the gap between knowledge and practice in the care of patients with RBDs by reporting clinical, laboratory, genetic and treatment information through an Internet database. Peyvandi et al reported data on 489 patients registered in the EN-RBD in 2012 highlighting the variability in RBD's with regard to coagulation factor levels and bleeding phenotype.[6] As this is the most comprehensive published data set on RBDs, numbers from HTC PP and Registry were compared to the EN-RBD figures.

3 | RESULTS

3.1 | Distribution of patients in HTC population profile vs registry

The HTC PP includes over 70 000 unique patients with a bleeding or clotting disorder. The HTC PP includes 9078 unique patients classified as having a rare clotting factor deficiency or an inherited or functional platelet disorder. Of these patients, 5452 had a primary diagnosis of a platelet disorder and were excluded from analysis. The remaining 3626 patients, or approximately 5.2% of all patients with bleeding and clotting disorders entered in HTC PP, had one of the following rare clotting factor deficiencies: Factor (F) I, prothrombin (FII), FV, FVII, FX, FXI, FXIII, combined FV + FVIII, Alpha 2 -Antiplasmin or Plasminogen activator inhibitor-1 (PAI-1). Collectively, these rare clotting factor deficiencies are referred to as RBDs. The Registry contains detailed information on 390 of these patients or 10.8% of the RBD patients in the HTC PP. By comparison, there are 22 511 unique patients with haemophilia (FVIII or FIX deficiency) in the HTC PP, and 9551 (42%) patients are included in the Registry. There were 147 patients in the Registry with multiple RBDs who were excluded from the analysis. Table 1 identifies the number of unique RBD patients by diagnosis in the HTC PP and the Registry compared to the number of haemophilia patients in each data set.

The majority 54% of RBD patients in HTC PP were female, and 79% were non-Hispanic white. African American, Asian, other races (including American Indians/Alaska Natives, Pacific Islanders/Native Hawaiian, multiple races) and patients with an unknown race comprised 11.4%, 3.6%, 1.8% and 4.3% of patients with an RBD, respectively. Similarly, of the 390 RBD patients represented in the Registry, 52% were female, and 75.4% were non-Hispanic white, 13.8% were African American, 6.1% were Asian, 2.3% were other races (including American Indians/Alaska Natives and multiple races), and 2.3% were of an unknown race.

3.2 | Expected numbers of RBDs based on US population compared to the HTC PP and registry

Based on the US population census, 325 719 178 individuals resided in the United States in 2017. Using reported prevalence rates from Orphanet for each disorder, the estimated number of affected individuals with each deficiency was calculated and compared to the number of cases included in the ATHN HTC PP (Table 2). An observed US prevalence rate based on the cases included in HTC PP was also calculated (Table 2). The number of cases reported in the HTC PP was lower than expected for FI, FII, FX, FV + FVIII by 36%, 61%,

75% and 94%, respectively (Table 2). The number of cases reported in the HTC PP was higher than expected for FXIII, FV, FVII, FXI by 7%, 14%, 33% and 185%, respectively (Table 2).

3.3 | ATHN Community Counts and the EN-RBD

The total number of patients captured in the HTC PP represents an almost fivefold increase over the total number of patients in the EN-RBD. The number of patients in the HTC PP that have detailed clinical data in the Registry, however, is 32% less than the total number of patients in the EN-RBD (Table 3).

4 | DISCUSSION

Leveraging the HTC PP and Registry to collect data on patients with RBDs represents an important step in improving healthcare delivery for the affected population in the United States. This is the first report of the US RBD population from the Community Counts national surveillance system and raises several important considerations. First, the prevalence of RBDs in the United States requires further study and investigation. Our analysis revealed significant variability in the percentage of the estimated population seen within the USHTCN; ranging from −95% to + 185% of the expected patient population. The USHTCN has been noted to serve between 67% and 82% of the US haemophilia population[9,10]; a disease state that has received notably more national attention, federal funding, and advocacy. It is, therefore, unlikely that the USHTCN cares for 100% of any RBD. The variability observed underscores the epidemiologic challenges inherent in all rare disorders, namely their rarity. Without systematic public health surveillance identifying all incident and prevalent cases and subsequent deaths, the published prevalence rates for many RBDs remain a rough estimate. The lack of healthcare provider knowledge, poor availability of reliable diagnostic assays and early mortality of patients with RBDs all result in under-diagnosis.[11] Undiagnosed patients and/or patients not suspected of having an RBD are not referred to federally recognized haemophilia treatment centres and, therefore, are not being included in national registries such as Community Counts. Conversely, the observed prevalence of some RBDs (FV, FVII, FXI, and FXIII) exceeds the estimated prevalence by 7%-185%. A variety of circumstances may have influenced the observed prevalence in our analysis, including migration of populations with a higher prevalence of specific disorders, improvement in specific quantitative diagnostic assays and improved survival associated with licensure of disease-specific clotting factor concentrates.

The second important consideration raised by our analysis is the potential impact of increased reporting and data capture in the Registry. Currently, only 10.8% of RBD patients in HTC PP have been included in the Registry. An increased number of patients in the Registry would facilitate a better understanding of various pathophysiological aspects of each disorder. RBDs are heterogeneous in their clinical presentation with bleeding symptoms ranging from non-bleeding phenotypes and minor post-traumatic bleeding to severe, spontaneous, life-threatening bleeding events. In specific deficiency states, the phenotypic correlation between residual coagulation activity and bleeding events is strong (FI, FXIII, FX, combined FV + FVIII); whereas in others (FV, FVII, FXI), we are uncertain

of the minimum residual coagulation factor level required to ensure normal hemostasis.[6] Increased enrolment in the Registry could help elucidate these thresholds or help identify other modifiers to predict clinical bleeding severity.

Low enrolment of RBD patients in the Registry may occur for a variety of reasons, including but not limited to: (a) the low frequency of HTC clinical encounters by RBD patients; (b) HTC staff perception that the Registry is targeted towards more common bleeding disorders and/or not tailored to meet data collection needs for RBDs; (c) RBD patient refusal to participate; and (d) limited HTC staff resources, hindering approaching all eligible RBD patients about potential enrolment. The public health implications of inaction warrant a coordinated response from the USHTCN. The opportunity to prevent morbidity and mortality related to delayed diagnosis and suboptimal treatment merits a systematic effort to increase the number of RBD patients enrolled in the Registry. This would enable the USHTCN to collect postmarketing safety data on newly licensed therapies and may encourage further clinical trials leading to licensure of specific products for the treatment of RBDs.

5 | LIMITATIONS

The main limitation of this analysis is the quantity and quality of data representing the RBD population. The diagnosis and collection of relevant laboratory and clinical data on RBDs must be obtained in a meaningful and systematic manner to advance our understanding of the severity, bleeding phenotype and appropriate treatment regimen. The 10.8% of RBD patients represented in the Registry may not be representative of the larger RBD population. Uniform diagnostic criteria and established, reliable, reproducible assays are imperative for creating standardized definitions of RBDs and ensuring data quality control across the United States. Quality assurance of data is key to reporting reliable national figures used to inform public health policies and guide action plans aimed at curtailing associated morbidity and mortality in RBDs. Orphanet, which we used as a source for global prevalence of RBD's, might be limited by the number of countries contributing their data (mainly Europe) and the quality of data reported, specifically, the validity of the RBD diagnoses. Thus, the expected numbers generated based on Orphanet prevalence rates might not be a true representation of the actual global prevalence rates for each condition. Despite the limitations, Orphanet is the best available and, to our knowledge, the most complete reference for rare disorders. A final limitation is the dearth of genetic testing available to conclusively diagnose RBDs, which further limits the conclusions that can be drawn from this analysis. This is an issue that ATHN is well positioned to address.

6 | CONCLUSIONS

Our analysis highlights various opportunities to leverage the Community Counts platform to elucidate gaps in the knowledge and treatment of patients with RBDs. A concerted national effort is needed to enrol patients with RBDs across the USHTC network into the Registry. Continued collaboration with European and other international colleagues will ensure ongoing harmonization of data collection and advancement of the shared goals of improvement in treatment and decreased disease associated morbidity and mortality.

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FIGURE 1.
Schematic of collaborating entities and components of Community Counts

TABLE 1

Number of rare bleeding disorder patients in the HTC population profile vs registry

Diagnosis	HTC PP	Registry	Registry/HTC PP (%)
Haemophilia A (FVIII)	17 115	7565	44
Haemophilia B (FIX)	5396	1986	37
Subtotal	22 511	9551	42
Factor I	207	25	12
Factor II	63	5	8
Factor V	371	22	6
Factor V and VIII	18	6	33
Factor VII	1444	155	11
Factor X	165	27	16
Factor XI	928	86	9
Factor XIII	175	44	25
Alpha 2 Antiplasmin	6	2	33
PAI-1	249	18	12
Subtotal	3626	390	10.8

Abbreviations: PAI-1, Plasminogen activator inhibitor-1; PP, Population Profile.

TABLE 2

Estimated vs observed prevalence of rare factor deficiencies[4]

Disorder	Published global prevalence[4]	Estimated US cases based on global prevalence	Observed US cases in HTC PP[a]	Observed US prevalence[b]	Observed vs expected number of US cases
Factor I	1:1 000 000	326	207	1:1 573 523	−36%
Factor II	1:2 000 000	163	63	1:5 170 146	−61%
Factor V	1:1 000 000	326	371	1:877 949	+14%
Factor VII	1:300 000	1086	1444	1:225 567	+33%
Factor X	1:500 000	651	165	1:1 974 056	−75%
Factor XI	1:1 000 000	326	928	1:350 990	+185%
Factor XIII	1:2 000 000	163	175	1:1 861 252	+7%
Factors V and VIII	1:1 000 000	326	18	1:18 095 510	−94%
Alpha 2 -Antiplasmin	<1:1 000 000	<326	6	1:54 286 530	NA[c]
PAI-1	Unknown	–	249	1:1 308 109	NA[c]

Abbreviations: PAI-1, Plasminogen activator inhibitor-1; PP, Population Profile.

[a]Cumulative Number of Patients Seen in USHTCN 1/1/2012–7/31/2017.

[b]Based on 2017 US Population of 325 719 178.

[c]Not applicable as the prevalence is not known.

TABLE 3

Rare disorder patients in EN-RBD compared to Community Counts

Disorder	EN-RBD	Registry (% of EN-RBD)	HTC PP
Factor I	46	25 (54%)	207
Factor II	6	5 (83%)	63
Factor V	60	22 (38%)	371
Factor VII	224	155 (69%)	1444
Factor X	45	27 (60%)	165
Factor XI	133	86 (65%)	928
Factor XIII	42	44 (105%)	175
Factors V & VIII	20	6 (30%)	18
Alpha 2 -Antiplasmin	–	2 (NA)	6
PAI-1	–	18 (NA)	249
Total	576	390 (68%)	3371

Abbreviations: EN-RBD, European Network of Rare Bleeding Disorders; PAI-1, Plasminogen activator inhibitor-1; PP, Population Profile.