TRAINEE SECTION

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Common bleeding disorders affecting individuals with Hereditary Hemorrhagic Telangiectasia

Abstract

Purpose: Hereditary Hemorrhagic Telangiectasia (HHT) is an autosomal dominant disorder affecting vasculature in different organ systems; seen at a rate of approximately 1:5000 in North America. Complications, with significant increases in health service utilization, arise from bleeding and shunts, and are particularly problematic in the lung and liver. Although these patients tend to chronically bleed from the GI tract and nasal cavities, a single bleed from arterio-venous malformations in the lungs or brain can have serious health implications and may be fatal. Bleeding due to vascular wall fragility in HHT patients can be further complicated with a concomitant bleeding disorder.

Methods: The proportion of adult patients seen in the Edmonton HHT center with a concomitant bleeding disorder, as assessed by blood test results for Factor VIII and related factors (Ristocetin Cofactor), Factor IX and Factor XI, was determined in a retrospective, single centre study.

Results: Of 77 individuals with HHT, four had below normal values of von Willebrand Factor, Ristocetin Cofactor or Factor VIII. Two patients had laboratory parameters diagnostic of a bleeding disorder, accounting for 2.6% of confirmed HHT subjects. These results indicate that establishing screening for bleeding disorders in HHT centers is important in managing bleeding symptomatology.

Conclusions: In individuals with HHT, the presence of a second bleeding disorder can have significant clinical implications on patient management and health care utilizations. This paper highlights areas that need to be reviewed with respect to best practice protocols for the management of HHT patients.

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Hereditary Hemorrhagic Telangiectasia (HHT), previously referred to as Osler-Rendu-Weber disease, is an autosomal dominant disorder with an estimated prevalence of 1 in 5000 North Americans [1, 2]. Clinical diagnosis of definite HHT requires at least three of the following criteria: a first-degree relative with HHT; the presence of mucocutaneous telangiectasiae; evidence of visceral arterio-venous malformations (AVMs); and, recurrent epistaxis [1]. Three genes have been found to be associated with HHT, which can be clinically evaluated for and include mutations in the ENG gene (chr. 9q34 "HHT1"), mutations in the ALK1 gene (chr. 12q13 "HHT 2") and, much less commonly, the SMAD-4 mutation (18q21) [2, 3]. Two additional loci (chr. 5q31 (HHT 3) and chr. 7p14 (HHT 4)) have been found to be associated with HHT but cannot be clinically evaluated at this time [2].

Manifestations of HHT include recurrent epistaxis (the most common symptom of HHT), telangiectasiae and AVMs in the gastrointestinal tract, lungs (pulmonary AVMs), brain (cerebral AVMs) and liver [1]. Telangiectasiae are smaller, thin-walled vessels that are dilated compared with normal vessels, while AVMs are direct arteriovenous connections that bypass the capillary bed [4]. Both types of vascular anomalies are under high pressure and, therefore, can be fragile, increasing the likelihood that the vessels will rupture and bleed at those locations [4]. While bleeding from visceral AVMs can have life threatening consequences, bleeding from mucosal telangiectasia (epistaxis and gastrointestinal tract bleeding) can significantly impact a patient's management as well as blood bank utilization due to transfusion dependence [5, 6]. As well, overall health service utilization can be impacted with requirements for increased ambulatory monitoring, intravenous iron infusions and blood transfusions.

In contrast to HHT-related vessel wall fragility, disorders such as Von Willebrand disease (VWD) and Hemophilia, which are caused by deficient clotting factors, can similarly affect an individual's propensity to bleed. VWD and Hemophilia are common bleeding disorders, with VWD occurring in up to 1 in 100 people and Hemophilia (A or B) affecting approximately 1 in 10000 males [7, 8]. Factor XI deficiency is another bleeding disorder and, although it is rare in the general population, it is seen at a much higher frequency in the Ashkenazi Jewish population (estimated to be 1 in 450 individuals) [9].

VWD is characterized by an inability to clot due to a deficiency of the glycoprotein von Willebrand factor [10]. Laboratory results from patients with VWD show decreased ristocetin-induced platelet aggregation due to reduced factor

VIII (FVIII) concentrations [11]. There are three main types of VWD, which are caused by mutations to the von Willebrand gene (chr. 12p13) and are differentiated by the mutant phenotype of the protein present in each case [12]. VWD types 1 and 3 show an autosomal dominant pattern of inheritance while VWD type 2 has shown an autosomal recessive pattern of inheritance in some cases [13, 14, 15].

Hemophilia is an X-linked recessive disease associated with an inability to form blood clots, resulting in prolonged bleeding [16]. Hemophilia A is caused by a mutation to the gene coding for factor VIII (FVIII) on chromosome Xq28 [16, 17] whereas Hemophilia B is caused by a mutation in the gene coding for coagulation factor IX (FIX) on chromosome Xq27 [17, 18].

Factor XI (FXI) deficiency, sometimes referred to as Hemophilia C, is a mild bleeding disorder caused by a mutation to the gene coding for FXI on chromosome 4q35.2, which results in reduced plasma levels of FXI [9, 19, 20]. FXI deficiency is normally inherited in an autosomal recessive pattern; however, a few specific mutations have been found to cause a dominant negative effect, resulting in an autosomal dominant pattern of inheritance in these families [9].

The co-occurrence of HHT and a bleeding disorder could result in severe blood loss and anemia, as bleeding would occur from both the fragile blood vessels associated with HHT as well as the deficient clotting factors associated with a bleeding disorder. Such HHT patients require clinical treatment and careful monitoring. Co-occurrence of acquired hemophilia and HHT was documented in a case report of a young woman who was identified as having both conditions after presenting with gross hematuria and being tested for FVIII inhibitors [21]. The patient in this case required clinical treatment as a result of the bleeding, emphasizing the potential risks associated with patients who have both HHT and a concomitant bleeding disorder [21].

This study sought to determine the prevalence of concomitant bleeding disorders in the HHT population seen through the Edmonton HHT center. Since HHT and the concomitant bleeding disorders examined in this study are not presumed to be co-inherited, then we would expect to find a similar rate of common bleeding disorders in the HHT population as in the general population. The clinical impact of these individuals in a health system would be quite profound and determining the prevalence of concomitant common bleeding disorders in the HHT population will help to identify this high-risk group and may result in modifications to screening protocols in HHT centers.

Additionally, some individuals with HHT are considered for anticoagulants due to stroke risk from deep vein thrombosis/venous thromboembolism or other causes and the risk benefit assessment needs to consider further bleeding.

Methods

This was a retrospective, single center study of all adult patients seen through the Edmonton HHT Center (209 patients) with a definitive diagnosis of HHT (98 patients) and institutional ethics approval to be included in the HHT database (78 patients). Patients with a suspected or confirmed diagnosis of HHT were approached at the Edmonton HHT clinic with information regarding the Edmonton HHT database and were asked if they would like to participate in the database. Patients who chose to provide informed consent were then eligible to be included in any study using the HHT database that obtained institutional ethics approval, including this study. Subject demographics (age and gender), genetic test results and laboratory results of clotting factor assays, captured in the Edmonton HHT database based on patient charts (from 2009-2014) and de-identified, were utilized in this study. The data was exported from the FileMaker Pro database to Excel to be analyzed.

All patients over the age of 18 years with a definite diagnosis of HHT and who were in the Edmonton HHT database were included in this study. A definite diagnosis of HHT is given to patients with at least three of the following criteria whereas patients are considered to have possible HHT if only one or two of the following criteria are met: a) first-degree relative with HHT, b) presence of mucocutaneous telangiectasiae, c) evidence of visceral arterio-venous malformations (AVMs) and d) recurrent epistaxis [1]. A definite diagnosis of HHT is also given if there has been molecular genetic testing [1]. Patients below the age of 18 were excluded from this study because most pediatric patients are not sent for bleeding disorder screening and, therefore, no data were available for these cases.

Not all patients with definite HHT, in the Edmonton HHT database, had been screened for bleeding disorders. Results available for any of the following blood tests were documented in the HHT database: Factor VIII and related factors (Ristocetin Cofactor and Von Willebrand Factor), Factor IX and Factor XI. All coagulation tests were performed on the STA-R Evolution analyzer using Stago reagents (Diagnostica Stago, Asnières Sur Seine, France) unless otherwise specified. Factor levels were performed using clot-based assays with three different dilutions per patient and the appropriate factor reagents (Factor VIII Deficient Plasma, Factor IX Deficient Plasma and Factor XI Deficient Plasma). The VWF assay used was an antigenic assay performed with Stago's LiaTest VWF:Ag kit. The Ristocetin Cofactor Assay serves as our functional assay of von Willebrand factor using a Chrono-Log model 470 VS 4 channel aggregometer, Ristocetin 10 mg/mL (Alpharma AS, Oslo, Norway) and lyophilized platelets (Biodata 101258, Horsham, PA, USA). If there were any concerns around false negative results from blood work, results were reviewed by a clinical hematopathologist (SN).

The following reference ranges were used for the bleeding assays: Factor VIII 0.50-1.50 U/mL, Ristocetin Cofactor 0.51-1.78 U/mL, Von Willebrand Factor 0.51-1.72 U/mL, Factor IX 0.50-1.50 U/mL and Factor XI 0.50-1.50 U/mL. Results were considered suggestive of a clotting deficiency if they fell below these reference ranges. The number of patients falling below each of these thresholds was calculated and compared with the total number of patients in each case.

Results

Out of 77 patients included in this study (Figure 1), four had low levels of at least one of the clotting factors examined on screening (Table 1), accounting for 5.2% of patients in our study. The breakdown of prevalence rates found among subjects in the study tested for the clotting factors are shown in Figure 1. Of the subjects tested for Ristocetin cofactor, 1.9%

TABLE 1. Demographics and blood test results for patients identified with a low value for at least one of the blood diathesis tested.

Patient	Gender	Ristocetin Cofactor (U/mL)	Factor VIII (U/mL)	Factor XI (U/mL)	VWF (U/mL)
1	M	0.18 (low)	0.53	Not Tested	0.27 (low)
2	F	0.53	1.09	Not Tested	0.49 (low)
3	M	1.06	1.18	0.52 (low)	1.04
4	M	1.03	0.28 (low)	Not Tested	1.2

FIGURE 1. Breakdown of subject numbers and clotting factor assay results showing the total number of patients in the database and the number of patients excluded based on various criteria. Also shown are the number of patients tested for each clotting factor and the number that presented low test results (referred to as positive for the screen). N = number of patients, VWF = Von Willebrand Factor, FVIII = Factor VIII, FIX = Factor IX, FXI = Factor XI.

had levels below the normal reference range, as did 3.7% of those tested for VWF. One patient had low values of both VWF and Ristocetin cofactor. Only one patient had been tested for factor XI and showed a deficiency, also only one patient was tested for Factor IX but with normal test results. On review of the results (Table 1), patient 1 and 4's laboratory parameters were diagnostic for the bleeding disorders, VWD and Hemophilia A, respectively, for a prevalence rate of 2.6% in the sample. The borderline levels for VWF and FXI in

patients 2 and 3 are not considered to be consistent with a bleeding disorder, but may merit further evaluation.

Discussion

This study showed that concomitant bleeding disorders were relatively common in patients with HHT, an association that may greatly impact bleeding rates and which underscores the importance of screening individuals with HHT. Earlier recognition of a concomitant bleeding disorder can impact how an individual with HHT is managed over time. The

chance inheritance of both these conditions can lead to a marked increase in health care utilization. We are not presuming a linked inheritance for these conditions but rather examining the overall impact of inheriting both disorders. Additionally as some of these individuals age, *the potential likelihood* for use of anti-platelet and anticoagulant therapies increases – which can have a negative impact on individuals with HHT who have a propensity to bleed.

This project expands upon work done on both bleeding within HHT populations and bleeding amongst individuals, with bleeding disorders as separate issues and examines them as a combined topic. Based on the prevalence rate of laboratory parameters diagnostic for a bleeding disorder of 2.6% found in our study, we estimate, given that the prevalence of HHT is 1 in 5000 North Americans, that at least 1 in 200000 North Americans may have both HHT and a common bleeding disorder. This finding of 2.6% in this HHT sample is higher than the bleeding disorder population estimates available in the literature [7, 8]. The most prevalent of the bleeding disorders included in this study, VWD and Hemophilia, have been quoted as having a prevalence of up to 1% for VWD in the general population and approximately 0.01% for Hemophilia amongst males in the general population [7, 8].

A limitation of this study is the fact that blood tests for each of the clotting factors were not available for all 77 individuals, resulting in a selection bias of individuals. Since it was a retrospective database project, we were limited to using the data that was already available. Patients with no available results were considered to be negative for a bleeding disorder in the total percentage of patients meeting diagnostic criteria for a bleeding disorder (2.6%). If all patients were tested, this percentage would either stay the same or increase; therefore, 2.6% can be considered a minimum estimate for the prevalence of bleeding disorders amongst this sample. As a follow-up to this study, it would be useful to perform a prospective study where all participants are given the full panel of blood tests. This study had a small sample size and lacked a control group with which to compare the prevalence of these bleeding disorders. Population estimates available for Hemophilia and VWD were used to provide a general comparison between the rates found in this study as compared with the general population.

If funding had allowed this project to be performed on a larger scale, this study could have been administered through a wider network, gaining a larger sample size and allowing for a more comprehensive review. Finally, a more detailed analysis of differences in testing between different laboratories would have been of value to examine.

This project has helped establish bleeding disorder screening protocols for the Edmonton HHT Center. It may also assist with developing further standard screening protocols for HHT in other centers (see Reference 1 for diagnostic guidelines). Some individuals with HHT may be given anticoagulants to reduce stroke risk; however, there has been debate as to the potential negative effects of this on individuals with HHT. A case review study by Edwards *et al.* found that 23% of HHT patients in their review reported severe complications while on anticoagulation therapy and 58% reported minor complications [5]. Some individuals with HHT have reported few negative outcomes with the use of anticoagulants, while others have experienced severe adverse effects. The negative clinical outcomes of anticoagulant use in HHT patients could be worse for individuals with both HHT and a bleeding disorder and, therefore, these individuals would require considerable monitoring if placed on anticoagulation therapy. The impact of coagulation disorders (DVT, thromboembolism, angina) and subsequent anticoagulation use if needed is already addressed in HHT Centers on a case-by-case basis. Modification of existing algorithms are implemented to stabilize the patient while minimizing long-term blood loss.

In conclusion, this study showed 2.6% of individuals with HHT in this sample were affected by a concomitant bleeding disorder. This sub-group of the population may require increased health resource utilization with regards to intravenous iron, factor concentrate and red cell transfusions. As such, it will be important to establish and improve upon current clinical standard protocols through HHT centers to identify and manage these individuals over their lifetimes.

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