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Evaluation of Diagnostic Criteria for von Willebrand Disease in Sudan

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Abstract:

Background: *von Willebrand disease is a bleeding disorder that is caused by deficiency or dysfunction of von Willebrand factor. People with blood group O have plasma von Willebrand factor antigen level 25 to 30 % lower than do non-O individuals. von Willebrand disease comprises a heterogeneous group of patients in whom the clinical diagnosis is often difficult because of a considerable intraindividual phenotypic variation and limited laboratory data, bleeding and family history. We are going to determine the blood group, bleeding history, the family history and the laboratory parameters supporting the diagnosis, to determine the criteria used to register a patient as affected with von Willebrand disease and to evaluate which particular diagnostic criteria are most relevant to clinical practice in Sudan.*

Methods: *We studied retrospectively a total of 139 patients diagnosed as von Willebrand disease and registered at The Khartoum Teaching Hospital, between 01/01/2011 and 31/12/2012.*

Patients data reviewed regarding personal bleeding history, family history, von Willebrand factor antigen level and blood group types.

Results: *Fifty seven (41%) of cases had blood group other than O, 40 (70.2%) of them gave positive family history. Sixty seven (48.2%)*

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of cases with blood group O had von Willebrand factor antigen level< 35 % and 15(10.8%) between 35% - 49 %. All cases had a positive bleeding history, 79.1% with history of mucosal bleeding and 1.4% with non- mucosal bleeding. The rest 19.4% of cases had positive history of both types of bleeding.

Conclusion: *This clinical study underlined the practical difficulties in the diagnosis of von Willebrand disease. The minimum criteria for diagnosis of von Willebrand (bleeding history, positive family history and low levels of von Willebrand factor for the blood group) were met in ninety-one (65.5%) of patients.*

Of the three parameters, the bleeding history was of prime importance in the clinical decision to diagnose and treat von Willebrand disease. The bleeding symptom typical of von Willebrand disease is mucosal bleeding.

We suggest the minimum criteria should be adopted for diagnosis of the disease: bleeding history, family history, low level of von Willebrand factor antigen for the blood group and von Willebrand factor ristocetin cofactor activity.

Key words: Von Willebrand Disease, von Willebrand factor antigen

Introduction

Von Willebrand disease (VWD) is the most common inherited disorder of primary haemostasis. It is very heterogeneous, both in its phenotype andgenotype.[1] The prevalence of VWD may be as high as 1 to 2% of the population, although many are never diagnosed; the prevalence of clinically evident VWD is much lower. No racial or ethnic predisposition has been determined. Both genders are affected, but there is a higher frequency of clinical manifestation in women.[2] In the triad of diagnostic criteria of VWD, bleeding Symptoms, low levels of von Willebrand factor (VWF) and inheritance pattern, usually autosomal dominant or recessive, bleeding history is recognized as the most critical issue. It is important to establish whether bleeding has been life-long or whether it is of recent onset,

indicating an acquired abnormality.[3] A positive family history compatible with the dominant forms of VWD requires that one first degree or two second degree relatives have a history of significant mucocutaneous bleeding and laboratory tests compatible with VWD.[4] In VWD, a number of genetic and nongenetic factors are likely to contribute to the wide variability of the clinical and laboratory phenotype. Most of the variation in VWF plasma is due to genetic factors, other is accounted for by the ABO blood group of the individual. In people with blood group O, VWF level is 25–35% lower than in non-O individuals. Thus, other unknown genetic factors may influence VWF levels and taken together with ABO blood groups and environmental effects such as physical and psychological stress, age, sex and hormones help explain the wide variety of VWD.[5] Clinical presentation with the appropriate phenotypic laboratory investigations is still the most accessible form of diagnosis considering the difficulties and high costs of molecular diagnosis; however, molecular diagnosis can be useful to confirm specific VWF defects in VWD families.

Methods:

We studied retrospectively a total of 139 patients diagnosed as von Willebrand disease and registered at The Khartoum Teaching Hospital, between 01/01/2011 and 31/12/2012. Patients data reviewed regarding personal bleeding history, family history, von Willebrand factor antigen level and blood group types.

The data was collected viaquestionnaire designed for this purpose and analyzed using the Statisticalpackage for social science program.

Results:

Fifty seven (41%) of cases had blood group other than O, 40 (70.2%) of them gave positive family history. Sixty seven (48.2%) of cases with blood group O had von Willebrand factor antigen level< 35 % and 15(10.8%) between 35% - 49 %. All cases had a positive bleeding history, 79.1% with history of mucosal bleeding and 1.4% with nonmucosal bleeding. The rest 19.4% of cases had positive history of both types of bleeding.

Discussion

We reviewed a population of 139 patients who had been previously diagnosed as VWD and analyzed the criteria that were used for diagnosis. As in the article by Federici, the bleeding symptom typical of VWD is mucosal bleeding. We found that the predominant type of personal bleeding was mucosal bleeding. (79.2%)[3] Only 67(48.2 %) of group O patients in our study had low VWF levels when adjusted for their blood group (VWF: Ag < 35 %). By definition, only these patients would have been eligible for a diagnosis of VWD. 51 (67.1%) of them exhibited the minimum criteria for diagnosis of VWD, and 16(23.9%) of the population qualified for a possible VWD diagnosis on the basis of positive bleeding but a negative family history.

Within the group of VWD patient blood group other than O (n=57), 40 (70.2%) exhibited the minimum criteria for diagnosis of VWD with both personal and a family bleeding history, and 17 (29.8%) of them considered possible VWD on the basis of positive bleeding and negative family history.

Of the original 139 patients previously diagnosed as VWD, 91 (65.5%) patients fulfilled the minimum criteria for diagnosis of VWD, and 33 (23.7%) would qualify for a possible VWD and need confirmation by genetic analysis. In our study, 15 (10.8%) of the population had blood group O and normal

value VWF: Ag (between 35 and 50%). They represent an indeterminate group, in whom the VWF: Ag level reduction comprises a mixture of genetic and non-genetic VWD causes. All those 15 patients had prolonged APTT, so they could be type 2 VWD or hemophilia. However, when the VWD diagnosis can neither be confirmed nor excluded and the risk of bleeding is unknown, empirical treatment is recommended.[6]

The possible VWD requires review family history, detecting an appropriate VWF mutation, and investigate about medical disorders that might cause acquired VWD such as lymphoproliferative, myeloproliferative disorders[7], nonhematologic malignancies[8] , drugs[9] [10] or hypothyroidism which cause reduction of VWF (15-45% levels). [11]

The ABO locus affects the level of plasma VWF, and the combination of VWF mutation and blood type O may be associated with bleeding symptoms. Blood group O alone could cause low levels of VWF and suggest a VWD diagnosis. It is estimated that about 20% of normal subjects experience excessive bleeding in a lifetime. [6] Bleeding symptoms and low levels of VWF alone are common and may occur together by chance, so 0.5% of all classified VWD patients are made on a chance combination alone.[12]

In our series of patients, 15(10.8%) Individuals with blood group O and VWF antigen levels between (35 - 50 %) did not have definitive VWD, but they were symptomatic. Moreover, this subgroup of patients had a similar bleeding pattern to the other groups of patients with blood type non-O and VWF levels between (35 - 50 %). On reviewing available literature, the use of ABO blood group is contradictory, so the ultimate diagnosis in difficult cases should include bleeding symptoms and confirmation by finding a genetic mutation. [13] [14]

Other investigators have also encountered similar problems with the definition and classification of VWD. Dean et al, reported difficulties in classifying a high percentage of

paediatric cases [15] , and Ingerslev & Gursel exemplified family studies that posed a diagnostic dilemma [16] .

Fressinaud et al described two patients with blood group O, VWF:Ag > 35 % and positive bleeding history as borderline normal subjects, because they could not be diagnosed using the highly sensitive PFA-100.[17]

In a recent ongoing study looking at the effect of adjusting the VWF levels for the blood group, about 30% of patients with menorrhagia had subnormal VWF levels, but nearly half did not fit the ABO-adjusted laboratory criteria for VWD. However, such patients had similar bleeding features and warranted consideration for similar therapies to the VWD patients. [14]

Due to difficulties in Sudan in doing multimeric analysis of von Willebrand factor, we suggest the following criteria should be adopted for diagnosis of VWD: bleeding history, family history, low VWF: Ag level for the blood group, and VWF: RCo.

This clinical study underlined the practical difficulties in the diagnosis of VWD. The minimum criteria for diagnosis of VWD (bleeding history, positive family history and low levels of VWF for the blood group) were met in ninety-one (65.5%) of patients.

The criteria should be adopted for diagnosis of VWD in Sudan should be includes bleeding history, family history, low VWF: Ag level for the blood group, and VWF: RCo.

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Figure (1): Total Number of Patients Classified according to their Blood Groups (Type O and Type Non- O) and the VWF LEVEL (VWF: Ag). (n= 139)

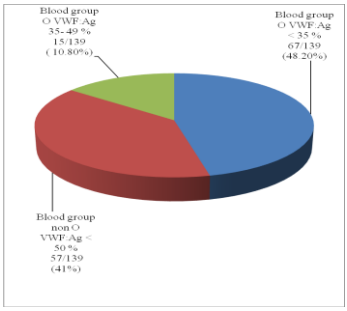

Figure (2): The Family History

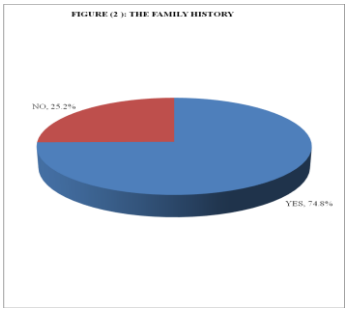

Figure (3): The First & Second Degree Relatives with Bleeding History.

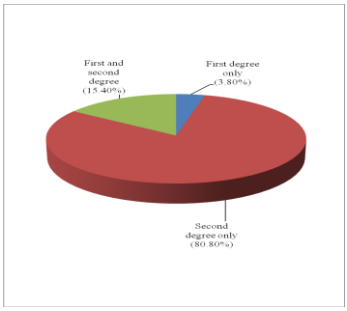

Table (1): Type of Personal Bleeding History. (n=139)

	Frequency	Percent
MUCOSAL	110	79.1
NON MUCOSAL	2	1.4
BOTH	27	19.4
Total	139	100.0

Table (2): Types of Bleeding History in Relation to the Different ABO Blood Groups.

(P=0 .881)

ABO BLOOD GROUPS	TYPE OF BLEEDING			TOTAL
	MUCOSAL	NON MUCOSAL	BOTH	
NON O GROUP < 50%	43 (75.4%)	1(1.8%)	13(22.8%)	57
O GROUP <35%	54(80.6%)	1(1.5%)	12(17.9%)	67
O GROUP 35% - 49%	13(86.7%)	0(0%)	2(13.3%)	15
TOTAL	110(79.2%)	2(1.4%)	27(19.4%)	139(100%)

Table (3): Positive Family History in Relation to the ABO Blood Subgroups.

ABO BLOOD GROUPS	POSITIVE FAMILY HISTORY		TOTAL
	YES	NO	
NON O GROUP < 50%	40(70.2%)	17(29.8%)	57
O GROUP <35%	51(76.1%)	16(23.9%)	67
O GROUP 35% - 49%	13(86.7%)	2 (13.3%)	15
TOTAL	104(74.8%)	35(25.2%)	139(100.0%)