DEVELOPMENT OF A WORKING DEFINITION OF SEVERE VON WILLEBRAND DISEASE

Tung Wynn, MD[1], Jeanette Cesta[2*], Robert F Sidonio Jr. MD, MSc[3*], Stefanie Dugan, MS[4*], Mona Sayedul Huq, PhD[1*], and Christopher Walsh, MD, PhD[5]

1 University of Florida, Gainesville, FL; 2 VWD Connect Foundation, West Palm Beach, FL; 3 Emory University School of Medicine, Atlanta, GA; 4 Versiti, Diagnositc Laboratories and Comprehensive Center for Bleeding Disorders, Milwaukee, WI; 5 Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

INTRODUCTION

von Willebrand disease (VWD) is a heterogeneous disorder resulting from abnormalities of quantity and function of von Willebrand factor (VWF). The primary symptom of bleeding may manifest differently ranging from mild to severe regardless of the subtype. The diagnosis and management of severe patients presents with challenges and may require a unique approach that is supported by the ASH ISTH NBDF WFH 2021 guidelines on the management of von Willebrand disease in its recommendation which states “In patients with VWD with a history of severe and frequent bleeds, the guideline panel suggests using long-term prophylaxis rather than no prophylaxis.”[1] Criteria identifying what constitutes a severe bleeding phenotype and severe disease has not been characterized as this may need to account for bleeding symptoms, plasma VWF levels, diagnostic VWD classification, and genetic findings, without meeting any specific standard.

AIM

To create a working consensus definition of severe von Willebrand disease which will allow for consistent identification and therefore improved and more effective care of this population.

RESULTS

Expert panel Composition.

- 23 individuals were identified, 17 experts agreed to participate
- 14 reside in North America, 2 in Europe, and 1 in Asia
- 12 physicians, 4 doctoral experts, 4 patients or family members, and 2 with other fields of expertise.

Consensus findings:

In the first round,

1) Genotype alone is currently not enough to establish a patient as having severe disease

2) No diagnostic classification of VWD was sufficient to determine severe disease

3) Any VWD type may be severe or be at risk for severe symptoms

a. Most Type 3 VWD are severe (but not all)

b. Many Type 2 VWD are severe

c. Some Type 1 VWD are severe.

In the second round,

1) A working definition of severe von Willebrand disease completed.

Common Variables Defining Severe VWD

	# articles found
Bleeding phenotype	
• Hemorrhagic symptoms	2
• Any(2) or Recurrent(1) use of factor replacement	4
Diagnostic Classification	
• Type 3	6
• Type 2b	1
• Any type 2 or 3, but only type 1 when <20%	1
Laboratory Testing	
• VWF Ag, VWF Act, Factor VIII <10% (2) < 20% (5) <30%(2) <40%(1)	10
Genetic Information	
• Genetic pathogenic variant(s) with Act <50%	1

Sources: Frederici 2004, Abshire 2015, Augusto 2004, ATHN 9: Severe VWD Natural History Study (ClinicalTrials.gov, NCT03853486), WIL–33 (clinicaltrialsregister.eu, 2020-004344-28), Vonvendi™ Surgical Study, rVWF Adult and Pediatric Prophylaxis Study, rVWF Ped prophy Study (clinicaltrial.gov, NCT05582993), WiN study: Netherlands study of moderate and severe VWD. Emicizumab for Severe VWD study (clinicaltrials.gov, NCT05500807).

Consensus Criteria Defining Those with Severe von Willebrand disease

A.	Anyone meeting a diagnosis of von Willebrand disease based upon the diagnostic classification of von Willebrand disease
	AND
B.	Any VWF antigen or activity:
	1. Result <20% regardless of bleeding phenotype
	Or
	2. Result <30% with excessive bleeding symptoms including:
	a. Bleeding that resulted in hospitalization, required surgical procedure, red blood cell transfusion, hemoglobin decrease >2g/dL, or
	b. Intracranial, intraspinal, pericardial, retroperitoneal, intramuscular bleeding with compartment syndrome, or
	c. Persistent or recurrent bleeding that is disruptive to social activities – in addition to work or school

METHOD

A modified Delphi method was selected to establish a consensus. The Delphi methodology as described by Maite B, et al [2] is a technique for reaching consensus about specific issues when empirical evidence is scarce or contentious. It achieves consensus about a specific topic by using several rounds of questionnaires to collect data from a panel of selected experts. A coordinating team assured that there was anonymity among the panel and provided a controlled feedback process after each round. Anonymity reduced the effect of any dominant individuals on other participants’ responses and controlled feedback encouraged experts to reassess their initial judgments based on the information provided. Modifications made included convening an initial meeting to establish the fields and identify the potential criterion within each field that would become the subject for questioning to focus the questionnaires and an electronic distribution of questionnaires and answers. Two rounds of questions were used. What is accepted as consensus was unclear, but it was defined for this project as when the lower bound of the 95% confidence interval showed a greater than 50% agreement.

CONCLUSIONS

von Willebrand disease is a heterogeneous disorder in which management and treatment of the group of patients with severe disease requires a very different approach; however, no specific or uniform standards exist for defining this patient group. This project creates a working consensus definition of severe von Willebrand disease, being vetted by ISTH SSC on VWD, which will allow for consistent identification and therefore improved and more effective care of this population. With a working definition, any gaps found with its use will encourage further research to improve upon it.

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REFERENCES

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CONTACT INFORMATION

Tung Wynn, MD. Associate Professor of Pediatrics, Division of Pediatric Hematology and Oncology. University of Florida, Gainesville, FL.