

AHCDC von Willebrand Disease Scientific Sub-Committee

Annual Report 2007-2008

Members

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Activities:

- a) The molecular basis of Type 1 VWD
- b) Quality of life assessment in VWD
- c) Von Willebrand disease in pregnancy
- d) The prevalence of symptomatic VWD in primary care
- e) The genetics of type 3 VWD
- f) Type 2B/Platelet type VWD Registry
- g) Prophylactic therapy for VWD

A. The molecular basis of type 1 VWD (Investigators: Drs Lillicrap and James)

Studies are ongoing in the Kingston laboratory to better define the molecular genetic mechanisms underlying type 1 VWD. A manuscript published in the Journal of Thrombosis and Haemostasis in September 2007 (Thromb. Haemost. 2007 Sep;5(9):1914-22) indicated that many cases of putative type 2M VWD did not have mutations in the GpIb binding domain of VWF and that only when the VWF:RCo:VWF:Ag ratio is <0.4 is there a strong likelihood of finding type 2M mutations. Additional studies are continuing to assess a variety of candidate transcriptional and splicing mutants found in type 1 VWD index cases.

B. Quality of life assessment in VWD (Investigator: Dr Barr)

This multicenter study evaluating the influence of VWD on QoL closed enrollment in 2007. Further financial support to enable analysis of the collated data has been obtained from the CHS. A final report should be forthcoming later in 2008 and a manuscript will be submitted to Haemophilia. When completed, this will represent the first large population study addressing quality of life issues in von Willebrand disease.

C. Von Willebrand Disease in Pregnancy (Investigator: Dr. Demers)

This study is co-sponsored with the Women's bleeding disorder sub-committee. The aim of the study is to characterize the levels of VWF and FVIII in normal women and women with VWD during and immediately after pregnancy. Post-partum blood loss is also being quantified through validated methods. This study is supported by the Canadian Hemophilia Society. A complete data set has been obtained from a cohort of normal pregnant women and attempts are being made to enroll more pregnant VWD women from other clinics to enable completion of the study.

D. The prevalence of symptomatic VWD in primary care (Investigators: Drs James, Silva, Rapson and Lillicrap)

Using a condensed version of the previously validated “Vicenza” bleeding questionnaire, a study had been completed to evaluate the prevalence of VWD in patients presenting to their primary care physicians in Kingston. Ten thousand subjects have been approached, and after administration of the bleeding questionnaire and repeat laboratory testing, a prevalence for symptomatic VWD of 1 in 1,000 has been demonstrated. This study has also allowed a prospective assessment of the condensed bleeding questionnaire. In an extension of this predominantly adult study, a similar survey is ongoing to evaluate the prevalence of symptomatic VWD in a large pediatric population. This study has added new pediatric-specific bleeding questions to the previously utilized abbreviated questionnaire.

E. The Genetics of type 3 VWD (Investigator: Dr. James)

This CHS-sponsored study is enrolling “nuclear trios” from families with type 3 VWD. The causative mutations in these families are being investigated in the reference laboratory in Kingston and the pattern of these mutations compared to the spectrum of mutations already documented in the Canadian type 1 VWD population. The study hypothesis is that the type 3 and type 1 mutations will show little overlap and that many more null mutations will be documented in the type 3 VWD population.

F. Type 2B-Platelet type VWD Registry (Investigators: Drs Othman and Lillicrap)

The differentiation between type 2B VWD and platelet type VWD (PT-VWD) is notoriously difficult with standard phenotypic studies. However, the treatment of the two conditions is distinct (VWF concentrates in type 2B VWD and platelet concentrates in PT-VWD). All cases of PT-VWD have, to date, been associated with heterozygous mutations in the Glycoprotein Iba gene which has a single coding exon. In contrast, all type 2B VWD mutations localize to exon 28 of the VWF gene. Thus, differentiation of these very similar disorders can readily be established by genetic testing using a stable and easily transportable substrate (genomic DNA). The Kingston mutation testing laboratory has now received additional supplementary funding to evaluate cases of phenotypically-defined type 2B VWD to see how many of these cases are in fact PT-VWD. This study is enrolling subjects from the international VWD community and is sponsored by the ISTH VWF SSC. There is also a new internet registry site containing detailed information about this disease (<http://www.pt-vwd.org/>).

G. Prophylactic treatment of VWD (Investigators: Drs Carcao and Winikoff)

A protocol for a new international multicenter study of prophylactic therapy in patients with VWD that experience recurrent mucocutaneous or musculoskeletal bleeding has been developed. The AHCDC has been represented in these discussions by Drs Carcao and Winikoff.