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Summary of a Nordic Workshop on von Willebrand Disease

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A B S T R A C T

This supplement to the journal Haematologica is a summary of a Nordic Workshop on von Willebrand disease held in Malmö, Sweden in August 2004. The meeting was a follow-up of the Nordic von Willebrand Symposium, held on Åland in September 1998 and, as such, was arranged by the Nordic von Willebrand group established after this symposium. Speakers from the USA, Germany, England, Denmark, Norway and Sweden covered different aspects of von Willebrand disease (VWD), from prevalence, classification and diagnostic aspects, to treatment and management.

Key words: von Willebrand disease, von Willebrand factor, desmopressin

VWD is the most common inherited bleeding disorder, yet many aspects are still unresolved, especially the diagnostic criteria and the genetic background to the most common form, type 1 VWD. A deficiency of the von Willebrand factor (VWF) causes VWD. The VWF is important for the formation of the platelet plug, binding platelets together and to the subendothelium. The VWF also protects coagulation factor VIII (FVIII) from inactivation in plasma. Deficiency of VWF causes bleedings as in VWD, whereas high levels may be prothrombotic, and may also be a marker for progressing atherosclerosis.[1] There are three main subtypes of VWD: type 1 is caused by a quantitative deficiency of VWF, type 2 by functionally defective VWF and type 3 by a total lack of VWF. Type 2 is further subdivided into types 2A, 2B, 2M and 2N depending on the nature of the qualitative defect.

Prevalence

At the meeting in Malmö, Erik Berntorp, Sweden, presented data covering the prevalence of VWD in the Nordic Region. Data from population studies has shown the prevalence of VWD to be about 1%[2,3] whereas the referral-based prevalence (including only patients diagnosed at specialized centers) is significantly lower, with estimates ranging from 23 to 113 cases per million inhabitants.[4,5] The estimated prevalence figure based on registered cases in the Nordic countries is 80 per million inhabitants. A broad variation in prevalence was seen among the Nordic Centers: type 1 (2.7-17.8), type 2 (0.2-4) and type 3 (0.2-1, with no patient in Iceland). Geir Tjønnfjord, Norway, presented data on the incidence of joint damage in VWD from the North American database from the Center for Disease Control (CDC). Joint bleedings are reported in all subtypes. In a cohort of 1282 females diagnosed with VWD, 3.1%, 0.6% and 3.6% of those with type 1, type 2 and type 3 VWD, respectively, had ever had a joint bleed. However, development of chronic joint damage was primarily seen in type 3 VWD.

The population studies may have overestimated the prevalence. By definition, 2.5% of the population have low VWF levels in plasma. Furthermore, bleeding symptoms are relatively common in the general population. Different surveys have shown that at least 25% of males and 46% of females have at least one bleeding symptom. Also high prevalence figures of family history for bleeding symptoms of up to 40-60% have been reported.[6] This may add up to a high prevalence in population studies, even if diagnostic criteria involving low levels of VWF, bleeding symptoms and a family history of bleedings or VWD are required. The diagnostic criteria for VWD type 1, presented by Jørgen Ingerslev, Denmark, are therefore under debate. The International Society on Thrombosis and Haemostasis (ISTH) subcommittee on VWF recently proposed provisional diagnostic criteria.[7]

Genetic background

The genetic background to type 1 VWD has hitherto been largely unknown and thus the presentations given by Ulrich Budde, Germany and Anne Goodeve, England, covering new developments in the classification and diagnosis of VWD were of great interest. Christer Halldén, Sweden, presented new knowledge on the genetic background of type 1 VWD in a Swedish population. There are probably several reasons for the difficulties in characterizing type 1. The VWF gene is technically difficult to study. It is located on the short arm of chromosome 12, is very large and spans 178 kb, has 52 exons and 51 introns.[8] A partially unprocessed VWF pseudogene is located in chromosome 22. The sequence spans exons 23-34 of the VWF gene (including intron sequences). In type 1, the protein has a normal function. Thus there are no functional defects that may help to indicate the position of any mutations in the VWF gene, in contrast to type 2 VWD. In types 2 and 3, mutations have been described in most cases. In the Nordic Workshop on VWD, two projects addressing this problem were presented. A European multicenter study supported by the European Union (EU) within the Quality of Life and Management of Living Resources Programme (1998-2003) is about to be finalized. The study entitled Molecular and Clinical Markers for the Diagnosis and Management of Type 1 von Willebrand disease (MCMDM-1VWD) was presented by Anne Goodeve. Twelve centers from 9 European countries recruited 154 families with a historical diagnosis of VWD type 1. This multicenter study has produced a large amount of data, which is still being evaluated (*http://www.shef.ac.uk/euvwd/*). A Swedish study conducted at the Department of Coagulation Disorders in Malmö has included about 50 families, both patients and relatives in a project that aims at describing the genetic background to VWD type 1. The main aims of this project, presented by Christer Halldén, are to identify genetic factors modifying the levels of von Willebrand factor both in the normal population and in families with von Willebrand disease type 1, to describe the genealogy of the von Willebrand factor gene region, and to correlate genotypic and phenotypic von Willebrand factor variables to bleeding symptoms.

Treatment

Different aspects of the pharmacological treatment of VWD were also reviewed. Treatment of VWD aims at normalizing the VWF activity in plasma, which can be achieved by stimulating the endogenous release of VWF with desmopressin (DDAVP, 1-desamino-8-D arginine vasopressin) or by infusion of a VWF concentrate. Desmopressin has long been said to be the first treatment option in type 1 VWD, but data is emerging revealing that this is true only for those with mild type 1. A recent European multicenter study, described by Stefan Lethagen, investigated the effect of desmopressin in patients with severe type 1 and 2 and showed that only a minority of patients with VWF activity < 0.10 kIU/L or FVIII activity < 0.20 kIU/L or bleeding time >15 minutes responded sufficiently.[9] Therefore, it is important to test the effect of desmopressin in such patients before clinical use. Patients who do not respond to desmopressin must be treated with VWF concentrates. Erik Berntorp, reviewed current treatment indications for VWF concentrates. There are several concentrates containing VWF that may, theoretically, be considered for use in VWD. However, as addressed by Stefan Lethagen, there are major differences in quality and specific activity between different VWF-containing concentrates. Concentrates lacking high molecular weight multimers of the VWF probably have a poor effect against mucous membrane bleedings. Concentrates with a high FVIII/ VWF ratio may cause dangerously high levels of FVIII in the patient, as the infused FVIII adds to the endogenously released FVIII made possible by the infusion of VWF. It is important for the treating physicians to be aware of the differences between concentrates so that inadvertent treatment failures or side effects can be avoided.[10] As dosing is increasingly based on VWF:RCo, as reviewed by Arthur Thompson, USA, it is important to take the specific activity and the ratio between FVIII and VWF content into consideration. An emerging issue in VWD is the need, in some cases, for prophylactic treatment, a subject covered by Pia Petrini, Sweden. The main indication for prophylactic treatment is joint bleeds in patients with type 3. Another important indication is treatment of recurrent mucous membrane bleedings, e.g. recurrent bleeds in patients with VWD and angiodysplasia.

In summary, von Willebrand disease is an intriguing disease. Many issues remain to be resolved, especially on diagnostic criteria and genetic background in type 1 VWD. Also, a continued improvement of haemostatic agents for patients with VWD is warranted.

Finally, the future of Nordic collaboration within VWD was discussed, focusing, under the guidance of Jørgen Ingerslev and Stefan Lethagen, on the question of whether a new classification system and Nordic Guidelines on diagnosis and management of VWD are required.

Concluding remarks

The Nordic Workshop on VWD in Malmö brought together experts, researchers and practicing physicians from Europe, the USA and, specifically, the Nordic Region in a sharing of knowledge that it is hoped will

stimulate progress in the field of VWD. A positive outcome of this meeting was the unanimous decision to continue the collaboration through the formation of a Nordic working group on VWD, with an aim to establish common Nordic guidelines for the diagnosis and treatment of VWD, as well as to evaluate the need for a Nordic patient registry on VWD. The meeting not only gave physicians throughout the Nordic Region the opportunity to establish contacts across borders, but also contributed to a better understanding of the disease and its treatment.

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References

1. Páramo JA, Beloqui O, Colina I, Diez J, Orbe J. Independent association of von Willebrand factor with surrogate markers of atherosclerosis in middle-aged asymptomatic subjects. J Thromb Haemost 2005;3:662-4
2. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood 1987;69:454-9.
3. Werner EJ, Broxon EH, Tucker EL, Giroux DS, Shults J, Abshire TC. Prevalence of von Willebrand disease in children: a multiethnic study. J Pediatr 1993;123:893-8
4. Shinmyozu K, Okadome T, Maruyama Y, Maruyama I, Osame M, Tara M. A study on the frequency of von Willebrand factor deficiency state. Rinsho Ketsueki - Jap J Clin Hematol 1991;32:67-8.
5. Cabrera ME, Artigas CG, Paez E, Monsalve V, Zolezzi P, Arauco G, Espinoza R, Hevia C, Villegas J. Von Willebrand disease in the IX Region of Chile. Revista Medica de Chile 1989; 117: 423-30.
6. Sadler JE. Von Willebrand disease type 1: a diagnosis in search of a disease. Blood 2003;101:2089-93.
7. Sadler JE, Rodeghiero F on behalf for the ISTH SSC subcommittee on von Willebrand factor. Provisional criteria for the diagnosis of VWD type 1. J Thromb Haemost 2005;3:775-7.
8. Mancuso DJ, Tuley EA, Westfield LA, Worrall NK, Shelton-Inloes BB, Sorace JM, Alevy YG, Sadler JE. Structure of the gene for human von Willebrand factor. J Biol Chem 1989;264:19514-27.
9. Federici AB, Mazurier C, Berntorp E, Lee CA, Scharrer I, Goudemand J, Lethagen S, Nitu I, Ludwig G, Hilbert L, Mannucci PM. Biologic response to desmopressin in patients with severe type 1 and type 2 von Willebrand disease: results of a multicenter European study. Blood 2004;103: 2032-8.
10. Lethagen S, Carlson M, Hillarp A. A comparative in vitro evaluation of six von Willebrand factor concentrates. Haemophilia 2004;10:243-9.