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Prevalence of von Willebrand disease in the Nordic Region

Erik Berntorp
Páll T. Önundarson

From the Department of Coagulation Disorders, Malmö University Hospital, Malmö, Sweden (EB); Department of Laboratory Hematology and Hemostasis Center, Landspitali University Hospital, Reykjavik, Iceland (PTÖ), on behalf of the Nordic Hemophilia Council

Correspondence: Prof. Erik Berntorp, Department of Coagulation Disorders, Malmö University Hospital, Malmö, Sweden. E-mail: erik.berntorp@medforsk.mas.lu.se

Von Willebrand disease (VWD) encompasses a wide spectrum of disease severity ranging from rare mild bleeding symptoms to severe hemorrhagic episodes that are similar to those of severe hemophilia. Due to this variation, the reported prevalence of VWD is a reflection of the criteria by which patients are identified. There are three subtypes of VWD. In type 1, the von Willebrand factor (VWF) is structurally normal, but has a plasma concentration that is subnormal, thus causing a bleeding diathesis. However, many subjects carrying the trait may have a normal VWF level and no increased bleeding tendency. Thus, type 1 VWD trait includes subjects carrying the hereditary marker who are phenotypically normal. Furthermore, levels of VWF may be low for other reasons than mutations in the VWF gene. It follows that there is a "grey zone" between the sick and the healthy and the definition of VWD type 1 can frequently be questioned.[1,2] This discrepancy between genotype and phenotype in type 1 VWD jeopardizes calculation of true prevalence figures as some physicians may include symptomatic subjects with low VWF who, genotypically, do not have VWD or asymptomatic individuals with low VWF. In type 2 VWD, the VWF is structurally abnormal. With the new tools of DNA technology it has become evident that some patients have previously been misclassified as type 1, whereas they now can be classified as type 2.[3] This discrepancy prevents accurate calculation of subtype prevalence, mainly of type 2 VWD, which is considered a rare disorder. In type 3 VWD, the VWF is absent from the plasma and platelets, and the factor VIII level is also very low. These patients are rare, but have severe bleeding symptoms and are usually in frequent contact with the health-care system. Based on the above considerations, the main uncertainty during prevalence estimation is the prevalence of type 1 VWD, although fine-tuning between type 1 and the rare type 2 may be difficult. Also, the method used to estimate prevalence is of major importance, i.e. using referral-based prevalence or population-based prevalence.

Referral-based prevalence

Referral-based prevalence is the number of patients seen at specialized centers divided by the total population served by those centers. Figures (per 100,000 inhabitants) range from 2.3 in Kagoshima, Japan[4] to 11.3 in the IX region of Chile,[5] with intermediate values reported in the UK,[6] Switzerland,[7] Jordan,[8] Venezuela[9] and Sweden.[10] Estimation of referral-based prevalence is subject to uncertainties such as the diagnostic capability of the centers and the true population count served by the centers. The true prevalence of VWD is probably higher than suggested by available estimates.

Population-based prevalence

When estimating population-based prevalence, the screening or population samples are used employing standardized criteria for symptoms, family history and laboratory values. Using this method, the combined prevalence of VWD and possible VWD per 100,000 inhabitants has been reported to be from 820 in northern Italy[11] to 1,600 in the USA.[12]

Prevalence in the Nordic Region

In the years 2003-2004, the Nordic Haemophilia Council surveyed the Nordic haemophilia centers using referral-based prevalence. The centers included were Aarhus and Copenhagen, Denmark; Helsinki, Finland; Gothenburg, Malmö and Stockholm, Sweden; Oslo, Norway and Reykjavik, Iceland. The estimated total population served was 20,840,000 and the total number of patients with VWD was 1,658 with the following figures according to subtypes: type 1 (n=1,456), type 2 (n=141) and type 3 (n=61). The estimated prevalence per 100,000 inhabitants was 8.0 (Figure 1), a figure that is intermediate according to published referral-based prevalence around the world, as cited above. As seen in Table

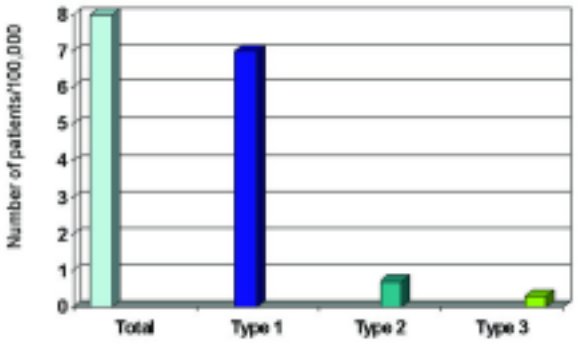

Figure 1. Referral based prevalence in the Nordic Region expressed per 100,000 inhabitants.

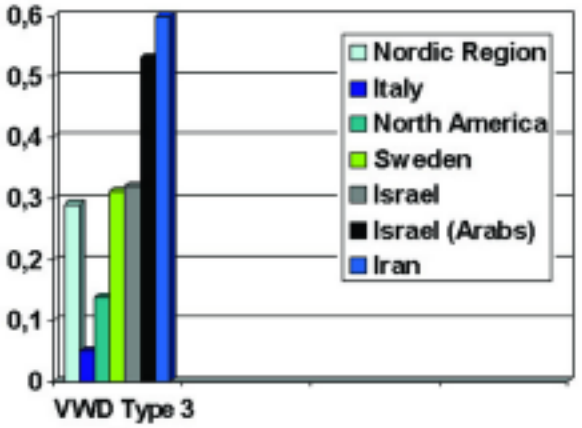

Figure 2. Referral based prevalence of VWD type 3, Nordic Region and published data.

Table 1. A broad variation in prevalence was seen among the Nordic Centers.

VWD	*Cases per 100,000*
Type 1	2.7-17.8
Type 2	0.2-4
Type 3	0.2-1

1, a broad prevalence range was seen among the Nordic centers. The figures probably reflect true prevalence differences among the rare cases of type 2 and type 3 VWD. However, the figures for type 1 VWD may reflect differences in diagnostic methods and registries between the centers rather than a genetic difference. Although some patients may have been diagnosed according to less strict criteria, not fulfilling VWD, the data indicates that many symptomatic cases have not been diagnosed in the Nordic area. The world-wide prevalence figures for type 3 VWD vary substantially as shown in Figure 2,[13-16] not least due to the fact that it is a homozygous recessive disorder and consequently the highest figures have been seen in countries where consanguineous marriages are more common.

Concluding remarks

The Nordic Haemophilia Council has undertaken a survey with the objective of estimating referral-based prevalence of VWD in the Nordic Region. The prevalence figures are in accordance with previous reports, but in such a homogenous geographic and socio-economic area as the Nordic countries, we see a broad variation of prevalence among centers. This probably reflects differences in diagnostics and registries between the centers rather than in genetics. Although some patients may have been over-diagnosed the data indicates that a number of symptomatic cases have still not been detected.

Our survey, like several previous studies, emphasizes that awareness of VWD, especially milder forms, should be increased among physicians who do not primarily work with bleeding disorders. It also points at the importance of using strict and uniform criteria when diagnosing VWD. Subjects with increased bleeding tendency will benefit from a correct diagnosis and subjects who are carrying the trait of VWD, but are phenotypically normal, will suffer from having a diagnosis but not a disease.

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