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Diagnosis and treatment of acquired von Willebrand syndrome

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ABSTRACT

Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder that is characterized by structural or functional alterations in von Willebrand factor (VWF) caused by a range of lymphoproliferative, myeloproliferative, cardiovascular, autoimmune, and other disorders. The pathogenic mechanisms responsible for the VWF abnormalities depend on the underlying condition, but include clearance due to binding of paraproteins, inhibition of VWF, adsorption to the surface of platelets, increased fluid shear stress, and resultant proteolysis or, more rarely, decreased synthesis. The diagnosis and treatment of AVWS are complicated by the need for multiple laboratory tests and the management of bleeding risk in a typically elderly population with serious underlying conditions that predispose towards thrombosis. Recently developed diagnostic algorithms, based on standard laboratory assays, may assist clinicians with the diagnostic workup and help differentiate between AVWS and von Willebrand disease (VWD) types 1 and 2. AVWS should be considered in all patients with new-onset bleeding whenever laboratory findings suggest VWD, particularly in the presence of an AVWS-associated disorder. AVWS testing is also recommended prior to surgery or an intervention with a high risk of bleeding in any individual with an AVWS-associated disorder. Treatment of the underlying condition using immunosuppressants, surgery, or chemotherapy, can lead to remission of AVWS in some individuals and should always be considered. Strategies to prevent and/or treat bleeding episodes should also be in place, including the use of VWF-containing factor VIII concentrates, desmopressin and tranexamic acid. Treatment success will depend largely on the underlying pathogenesis of the disorder.

Acquired von Willebrand syndrome (AVWS) is a rare bleeding disorder that can be defined as any structural or functional alteration in von Willebrand factor (VWF) that is not inherited and causes bleeding. The diagnosis and treatment of AVWS are complicated by the need for many different laboratory tests to help differentiate between AVWS and some subtypes of congenital von Willebrand disease (VWD), with management of bleeding risk often confounded by the presence of serious underlying conditions in populations at increased risk of thrombosis.

The prevalence of AVWS remains poorly defined, since less than 700 cases have been reported in the world literature (Table 1) [1–3]. Federici et al. were the first to review the literature (1968–1999), identifying 266 cases of AVWS characterized by reduced plasma levels of VWF [1]. An additional 186 patients were detected via the establishment of an international registry by the International Society on Thrombosis and Haemostasis (ISTH) [1].

Table 1
Overview of studies assessing the epidemiology of acquired von Willebrand syndrome (AVWS) [1–3].

Source	Cases	Denominator	Reference
Literature survey (1968–1999)	266	?	[1]
ISTH Registry (2000)	186	?	[1]
German reference laboratory (2000, over 2 years)	187	5,014 samples	[2]
Hannover cohort (2008, over 10 years)	35	1,500 patients	[3]

ISTH, International Society on Thrombosis and Haemostasis.

In subsequent years, a further 187 cases of AVWS were found by a reference laboratory in Germany amongst 5,014 plasma samples from patients with symptoms of defective primary hemostasis [2], with 35 new patients from a sample of 1,500 individuals with acquired bleeding described in 2008 [3]. Although these studies do not allow us to estimate the true prevalence of AVWS, they confirm that, although rare, a rate of one case of AVWS in every 30–40 samples from patients with bleeding disorders [2,3] suggests the condition is certainly one to consider in daily hematologic practice.

Risk factors for AVWS

What these landmark epidemiologic studies did help to establish was the type of patient most likely to be at risk of developing

Abbreviations: AVWS, acquired von Willebrand syndrome; FVIII, factor VIII; HMW, high molecular weight; IgG, immunoglobulin G; ISTH, International Society on Thrombosis and Haemostasis; MGUS, monoclonal gammopathy of undetermined significance; rFVIIa, recombinant activated factor VII; VWD, von Willebrand disease; VWF, von Willebrand factor; VWF:Ag, VWF antigen; VWF:CB, VWF collagen binding; VWF:RCo, VWF:risocetin cofactor.

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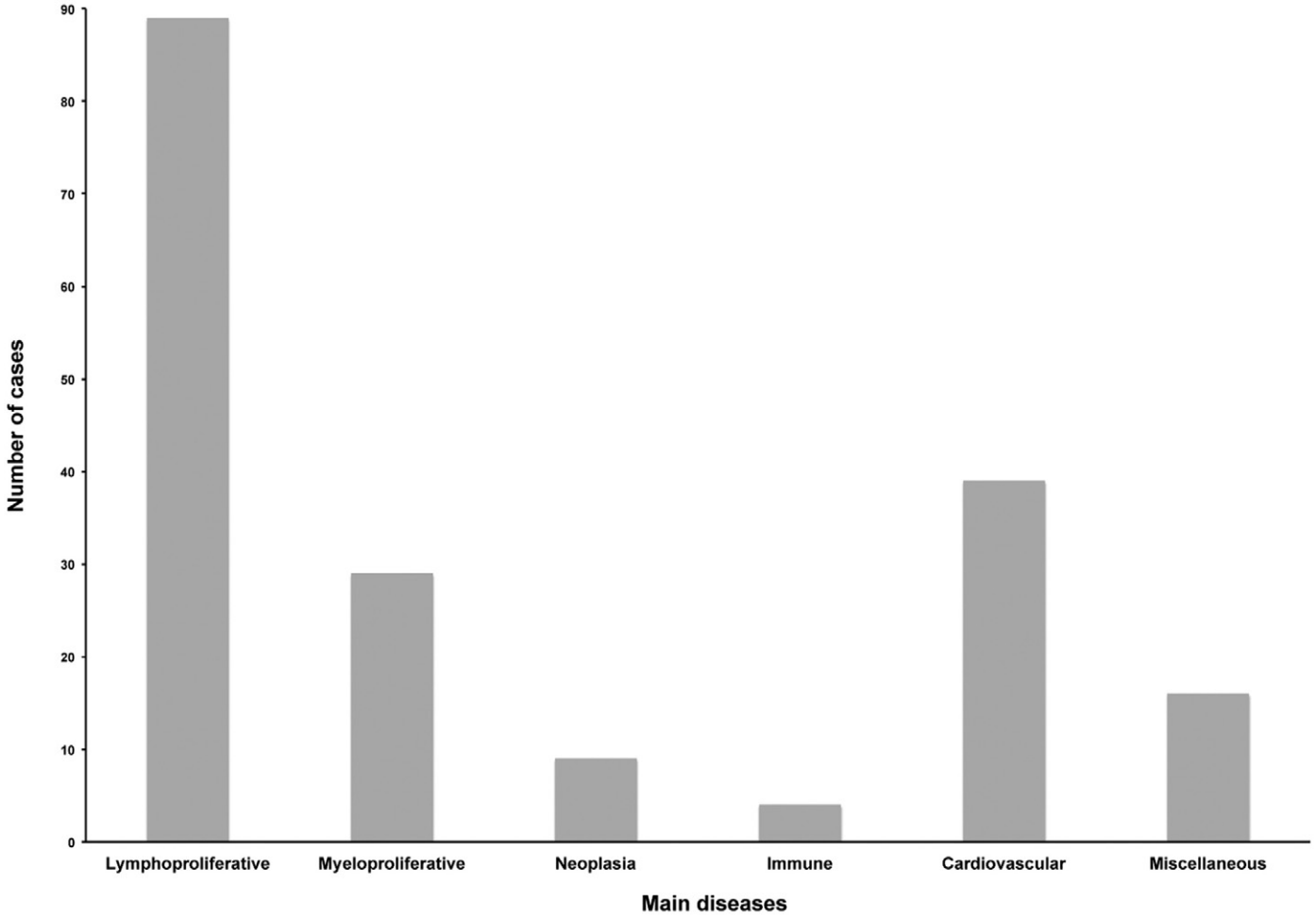

Fig. 1. Frequency of underlying conditions associated with acquired von Willebrand syndrome in 186 patients identified in an ISTH registry [1]. Miscellaneous conditions include infectious diseases, other systemic diseases, drug-induced and idiopathic diseases. ISTH, International Society on Thrombosis and Haemostasis.

AVWS. The ISTH registry [1] found the highest frequency of AVWS in elderly patients, reporting a median age at diagnosis of 62 years (range 2–96 years). The registry also identified that the highest rate of AVWS was in patients with lymphoproliferative disorders (affecting 48% of patients in the registry) – most notably monoclonal gammopathy of undetermined significance (MGUS) (affecting 23% of registered patients) (Fig. 1). Congenital and acquired cardiovascular defects, including atrial septal defects and aortic stenosis, were reported in 21% of patients in the registry. Other reported underlying conditions included myeloproliferative disorders (e.g. essential thrombocythemia) and neoplasia. Autoimmune disease, hypothyroidism, and uremia were also found to be risk factors in a small percentage of patients.

Later reports suggested an increase in the contribution made by cardiovascular disorders to the incidence of AVWS, rising from 21% of patients in the ISTH registry, to 40% of patients in the study by Budde et al. [2], and to 45% of patients in our Hannover cohort (reported in 2008) [3]. This apparent increase in frequency may be due to differences in the inclusion criteria used in each study or to increasing awareness of AVWS amongst cardiologists. It may also be due to an increased use of left ventricular assist devices, which are being used more frequently to sustain heart failure patients awaiting heart transplantation, and which are now known to be associated with a high risk of developing AVWS [4–6].

Pathogenesis of AVWS

The defects in VWF structure or function associated with AVWS depend primarily on the underlying cause of the condition (Table 2). In lymphoproliferative disorders such as MGUS and in some cancers, autoimmune clearance due to binding of paraproteins or inhibition of VWF results in very low circulating concentrations of the protein [7–14]. AVWS associated with myeloproliferative disorders is most likely due to increased binding of VWF to

Table 2
Pathogenic mechanisms responsible for structural or functional disturbances of von Willebrand factor (VWF) in different acquired von Willebrand syndrome-associated conditions.

Reduced VWF synthesis	Inhibition/clearance by paraproteins or autoimmune inhibitors	Adsorption of VWF high-molecular weight multimers	Increased shear stress and proteolysis
• Severe hypothyroidism • Drugs (e.g. valproic acid)	• B cell lymphomas • Monoclonal gammopathy of unknown significance • Multiple myeloma • Autoimmune disorders	• Myeloproliferative neoplasias (essential thrombocythemia, polycythemia vera) • Thrombocytosis (non-malignant) • Other malignant disorders	• Aortic valve stenosis • Artificial heart valves • Left ventricular assist devices • Other (mostly congenital) heart defects with disturbed flow