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Acquired Willberand Syndrome and Acute Coronary Syndrome: Risks and Management

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Abstract **Review Article**

Von willbrand syndrome remains a rare pathology. Its etiologies and clinical manifestations are varied. This syndrome can be inherited or acquired. The acquired form is associated with various pathologies (Gastric, mechanical support system…) including cardiovascular diseases such as aortic stenosis, HCM, and Mitral regurgitation. Nevertheless, the association of acquired Willebrand syndrome with coronary pathology remains a rare association. In this literature review, we have made a review of the various articles addressing this subject. The management of ACS in patients with AvWS follows that of normal patients in terms of interventional procedure, however therapeutic drug management remains delicate given the hemorrhagic risk that these drugs present. The use of DAPT and heparin is possible while thrombolysis remains at very high risk for the patient. The use of desmopressin can be done with caution and also factor VIII and vWF concentrates have their place to reduce the risk of bleeding. Overall, the collaboration of the cardiologist and hematologist remains essential for better management of these patients.

Keywords: Von willbrand syndrome, Gastric, cardiovascular diseases, heparin, desmopressin.

INTRODUCTION

Von willbrand syndrome remains a rare pathology. Its etiologies and clinical manifestations are varied. this syndrome can be inherited or acquired. The acquired form is associated with various pathologies (Gastric, mechanical support system…) including cardiovascular diseases such as aortic stenosis, HCM, and Mitral regurgitation. Nevertheless, the association of acquired Willebrand syndrome with coronary pathology remains a rare association that deserves to be brought to light with its different consequences and way of management.

DISCUSSION

Von willebrand factor is a large multimeric glycoprotein present in plasma and synthesized in weibel-palade bodies in endothelium, megakaryocytes and Alpha-granules and sub endothelial connective tissue. Its function is to bind with plasma proteins, essentially factor VIII and ensure blood coagulation. Inactive Factor VIII associates with VWF in the circulation, if this binding has not taken place, it degenerates quickly. When clotting is stimulated platelet receptors are activated. The VWF associates with these activated receptors. VWF associates with the platelet glycoprotein Ib (GPIb) receptor and forms a complex with glycoprotein IX (GPIX) and glycoprotein V (GPV). This occurs when there is a rapid flow in narrow blood vessels [1].

Von Willebrand disease is a rare pathology with various manifestations and causes. It can be inherited or acquired. There are three types for inherited Willbrand syndrome: Type 1 caused by partial quantitative deficiency of von Willebrand factor, Type 2 caused by several qualitative defects in von Willebrand factor. type 3 related to a complete quantitative defect of the von willebrand factor [1].

Acquired von Willebrand disease occurs when secondary (acquired) processes lead to a functional impairment of von Willebrand factor, either by decreasing its available quantity or interfering with the

physiological hemostasis pathway. Its prevalence is estimated at 1% of the world population with clinically significant forms of 125 per million. The prevalence of the aquice form of this syndrome constitutes 1 to 5% of all its forms combined [2].

The pathophysiology of acquired vWF deficiency often remains incompletely explored and therefore poorly elucidated in the majority of patients with AvWS. In contrast to congenital vWD, vWF is synthesized normally in most patients with AvWS, however it is rapidly removed from plasma through different pathogenic mechanisms, which results in decreased circulating levels of vWF [3]. Three main mechanisms have been demonstrated to account for AvWS: circulating autoantibodies to vWF adsorption of vWF onto tumoral or activated cells and proteolytic degradation of vWF. Each of these mechanisms may be common to several underlying disorders and each disease may involve one or more mechanisms [3].

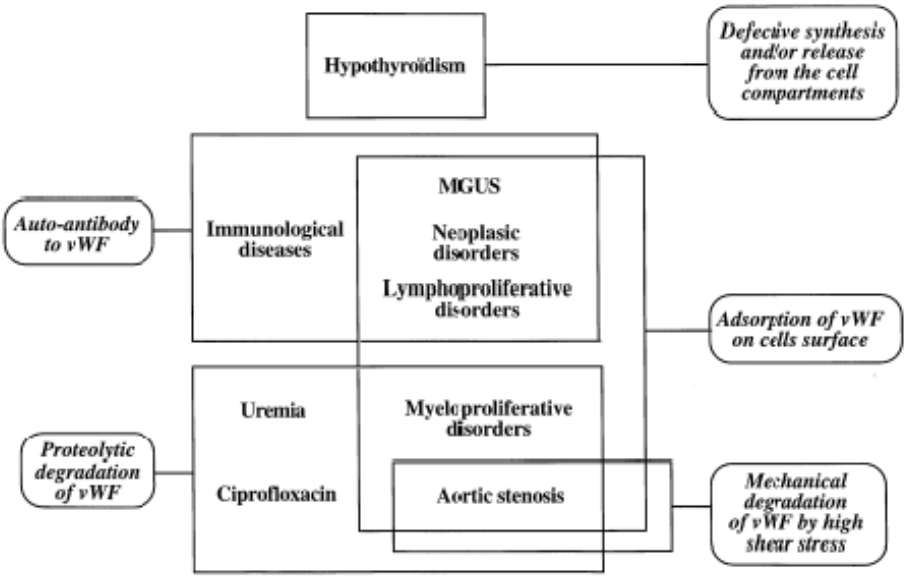

Figure 1: Pathophysiology for acquired von Willebrand syndrome (AvWs) [3]

Van Willbrand syndrome can be presented in a variable way either in the form of epistaxis or hematomas of variable localizations. Prolonged bleeding from benign wounds or from the oral cavity or heavy menstrual bleeding are frequently present. Gastrointestinal bleeding occurs rarely. Other manifestations may occur as easy bruising or severe bleeding after surgical procedures or exacerbation of bleeding symptoms after ingestion of aspirin [4]. The bleeding tendency was recently suggested to depend on the pathogenic mechanism of AvWS, and appears to be more significant in patients with auto-antibodies to vWF or with a decreased level of platelet vWF [5].

Initial evaluation for VWD requires a combination of screening tests, as no single test can confirm the presence of fully functional VWF. Along with assessment of VWF protein presence, routine screening tests include assessment of VWF–platelet and VWF–FVIII interactions [6].

At minimum, three tests are included in the current standard practice for laboratory diagnosis of VWD. These include von Willebrand factor antigen level (VWF:Ag), von Willebrand factor activity (VWF: Act or VWF: RCo) level, and circulating level of FVIII (FVIII:C) [7].

The diagnosis of AvWS is carried out in two stages: the first phase is to established the positive diagnosis of vWD (assay of vWF:RCO, vWF:CB, vWF:Ag, FVIII:C, study of the distribution of multimeters), and the second phase is to prove the acquired nature of the deficit and to specify its phenotype [8].

Currently, there is no sensitive and specific diagnostic test for AvWS. The minimum criteria defined by the international registry are: demonstration of the acquired nature of bleeding; reduction of vWF:RCO or vWF:CB; vWF:RCO/Ag or vWF:CB/Ag ratio less than 0.7 if the second condition is not met but only in the event of bleeding problems.

Numerous diseases have been reported in association with AvWS (Table 1), most of which are clonal hematoproliferative diseases [5].

Table 1: List of disorders associated with acquired [5]

CLONAL HEMATOPROLIFERATIVE DISEASES	NEOPLASIA	OTHER DISEASES
a- Monoclonal gammopathies (MG) : - MG of undetermined significance - Multiple myeloma - Waldenström macroglobulinemia b- Lymphoproliferative disorders : - Chronic lymphocytic leukemia - Non-Hodgkin's lymphoma - Hairy-cell leukemia c- Myeloproliferative disorders : - Essential Thrombocytemia - Polycythemia vera - Chronic granulocytic leukemia d- Acute leukemias : - Acute myelocytic leukemia - Acute myelomonocytic leukemia - Acute lymphocytic leukemia	- Wilm's tumor (nephroblastoma) - Adenocarcinoma of the stomach - Adrenal cortical carcinoma - Peripheral neuroectodermal tumour (PNET) **IMMUNOLOGICAL DISEASES** - Systemic lupus erythematosus (SLE) - Hypothyroidism - Scleroderma - Mixed connective tissue disease - Graft-Versus-Host disease (GVH)	- Uremia - Aortic stenosis - Mitral valve prolapse - Congenital cardiac defects - Gastrointestinal angiodysplasia - Epstein Barr Virus infection - Hydatic cyst - Ehlers Danlos syndrome - Lactoferrin deficiency - Hemoglobin E-β0 thalassemia **DRUGS AND AGENTS** - Antibiotics : Griseofulvin, Ciprofloxacin - Anticonvulsants : Valproïc acid - Plasma Volume Expander : Hydroxyethyl starch (HES)

There is a close relationship between van willbrand factor and coronary heart disease. ACS is caused by rupture of atherosclerotic plaques, exposure of subendothelial procoagulant factors, and subsequent thrombus formation leading to myocardial ischemia. VWF is fundamentally involved in this process. It supports platelet adhesion to the subendothelial matrix of injured vessel walls, enhances platelet aggregation, and promotes fibrin clot formation [9]. Furthermore, detection of VWF in fresh, human coronary thrombi suggests a causative role of VWF in platelet thrombus growth [9].

Many studies have shown that high levels of plasma vWF are associated with risk of coronary heart disease and increased levels of vWF have been found in patients with acute myocardial infarction. Probably, this elevation of vWF level is also seen in vWD patients presenting with ACS as evident by their baseline and ACS vWF levels in case reports. vWF levels rise in ST-elevation myocardial infarction (STEMI) up to 1.5-2 fold in the frst 24 hours and peak at 48 to 72 hours, with levels returning to baseline within 14 days [10].

The management of an acute coronary syndrome in patients with acquired von willebrand syndrome remains a delicate dilemma, especially given the use of antithrombotic and antiplatelet drugs which may increase the risk of bleeding in this type of patient.

In fact, Aspirin treatment results in a minor decrease in vWF levels and significantly prolongs bleeding time only in patients with less prevalent severe vWD type. multiple reports have described use of heparin in vWD patients undergoing PCI and cardiac surgery without siginifcant bleeding complications [10].

Thrombolytic therapy can degrade vWF, further reducing the levels and increasing bleeding risk and therefore increases the risk of bleeding in patients with VW syndrome [11].

American Society of Hematology in its recommendations for the management of patients with von willebrand syndrome suggests that In patients with VWD and cardiovascular disease who require treatment with antiplatelet agents or anticoagulant therapy, giving the necessary antiplatelet or anticoagulant therapy is better over no treatment at all [12].

There are two main therapies available for treatment of spontaneous bleeding episodes and for bleeding prophylaxis: desmopressin (DDAVP) and factor VIII/vWF concentrates [10].

Rathore *et al.*, proposed a management protocol for patients with acute coronary syndrome and Von willebrand syndrome.

If a recent vWD assessment, including typing, vWF activity, and factor VIII levels, is available, these can help in making decisions. vWF activity levels greater than 30% in vWD patients are considered safe for minor surgery. However, given the prognostic urgency of using DAPT in ACS, it is reasonable to proceed with caution in initiating these therapies in patients with ACS-vWD. We suggest antiplatelet therapy can be given with aspirin and clopidogrel in both STEMI and unstable angina and NSTEMI in vWD patients, as 75% of them are type 1 vWD [10].

The indications for cardiac interventions for patients with VWs are the same as for normal subjects. PCI is always first-line. For UA and NSTEMI, where more time is available, heparin in addition to dual-antiplatelet therapy can be given. Hematological consultation and factor levels may be considered unless a decision for urgent PCI is made. In case of urgent PCI, follow the STEMI track.

The recommendations of the ESC 2020 recommend favoring the arterial approach over the femoral approach to reduce the risk of bleeding and also to shorten the duration of the DAPT according to the calculation of the risk of bleeding by certain scores such as the HASBLED or the ARC-HBR .GP IIb/IIIa antagonists should be considered for bail-out if there is evidence of no-reflow or a thrombotic complication [13].

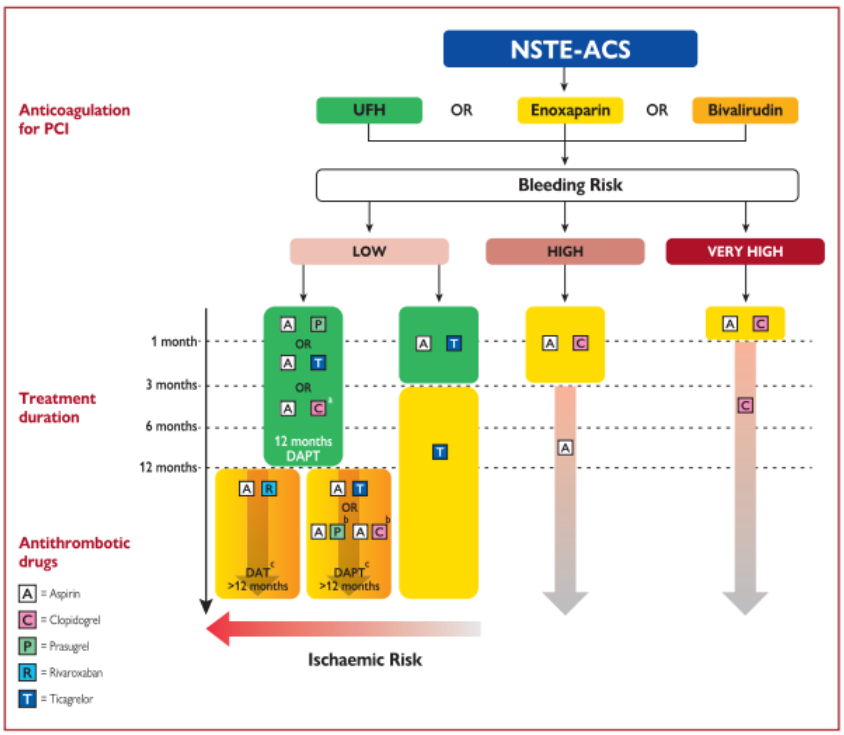

Figure 2: European recommendations for shortening the duration of DAPT in the event of a high risk of bleeding or ischemia [13]

Desmopressin can be used periprocedurally to increase factor VIII and von Willebrand factor levels, although this increases the risk of thrombosis and hypertension [10]. Actor VIII/ vWF complex, a commercially available concentrate, can also be used in consultation with a hematologist [10].

Factor VIII and vWF levels should be checked during the ACS if available in the hospital, as well as after 4-6 weeks to guide long-term antiplatelet therapy with hematological consultation. Close outpatient followup and patient education are necessary [10].

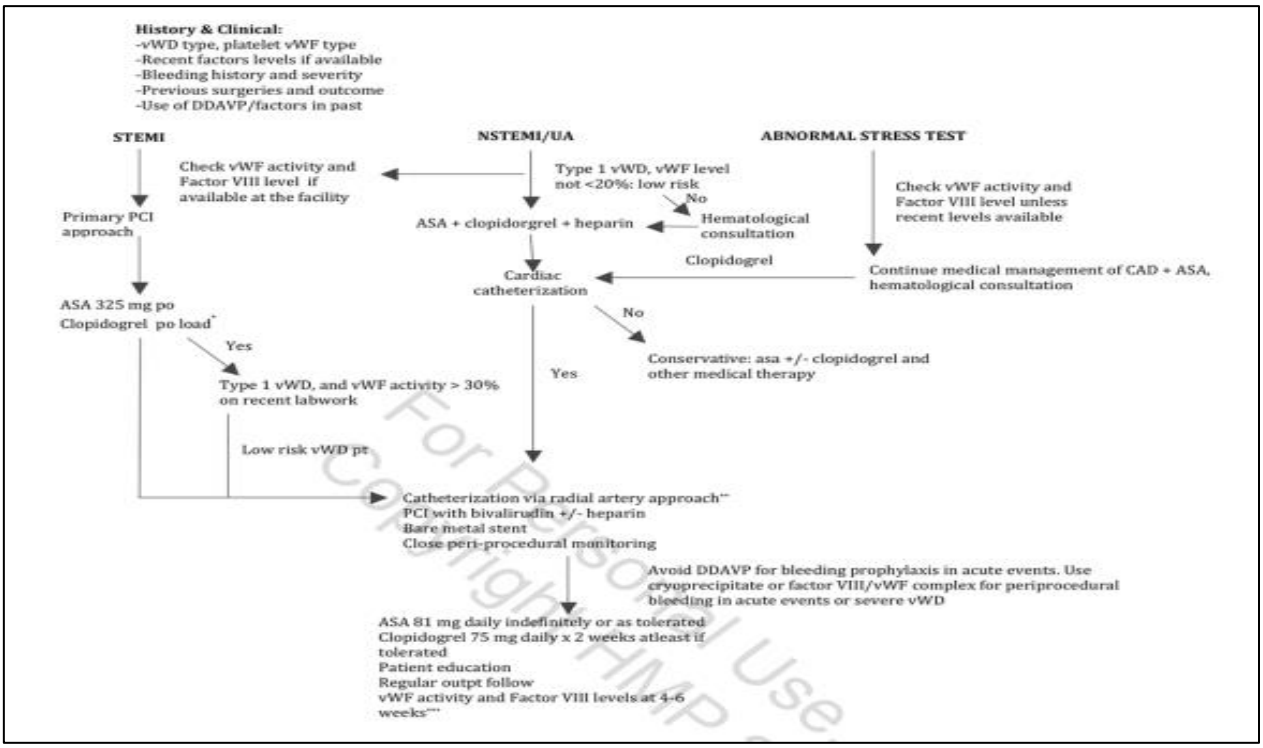

Figure 3: Management proposal of acute coronary syndrome in vWD patients by Rathore *et al.*, [10]

CONCLUSION

Acquired Willebrand syndrome remains a rare bleeding disorder with an underestimated frequency with consequences that can be fatal in certain situations. In the majority of cases the AvWS is associated with various underlying diseases among them acute coronary syndromes. The association of these two entities remains rare but very difficult to manage. The management of ACS in patients with AvWS follows that of normal patients in terms of interventional procedure, however therapeutic drug management remains delicate given the hemorrhagic risk that these drugs present. The use of DAPT and heparin is possible while thrombolysis remains at very high risk for the patient. The use of desmopressin can be done with caution and also factor VIII and vWF concentrates have their place to reduce the risk of bleeding. Overall, the collaboration of the cardiologist and hematologist remains essential for better management of these patients.

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