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Von Willebrand disease and antiphospholipid antibody syndrome

Von Willebrand disease (vWD) is a common inherited hemorrhagic entity first described a century ago due to defects or deficiencies in the von Willebrand factor (vWF); management includes the replacement of vWF and additional therapies for some cases and recent guidelines emphasize mutation patterns in subgroups and patient-reported outcome (PRO).[1–5] The evidence-based guidelines of vWD diagnostic criteria were developed in 2021, including personal and family history of excessive mucocutaneous bleeding and low vWF blood level.[3] A retrospective study included 30 patients and 76.7% underwent routine recombinant vWF (rvWF) prophylaxis for a mean time of 2.9 years; the annualized bleed rate (ABR) and total and bleed-related inpatient visits and the number of surgeries decreased during the use of rvWF.[1] The authors concluded that patients receiving routine rvWF prophylaxis demonstrated less ABR and healthcare resource utilization (HCRU) compared with the baseline period, indicating that rvWF prophylaxis may result in improved outcomes among people with vWD across all subtypes.[1] A narrative review up to September 2024 evaluated nonstandard or emerging therapies for vWD, as FVIII replacement or antibody-based FVIII bypassing strategies (emicizumab) that may be useful as an initial option in some cases, including the 2N or 3 vWD types, or those with inhibitors; emerging therapies may be useful, including hemostasis rebalancing agents.[2] The authors highlighted the option of personalized treatments, meaning potentially distinct managements for different vWD patients, or for given patients accordingly to treatment aims.[2] A cross-sectional study about vWD in the Netherlands utilized a questionnaire on the experienced severity of vWD (4-point scale), bleeding score (BS), and quality of life (QoL), including 736 individuals with a median age of 41.0 years, and 59.5% of them were females.[4] A total of 443 had type 1, 269 type 2, and 24 type 3 vWD, the self-reported severity was severe (n=52), moderate (n=171), mild (n=393), or negligible (n=120); female, type 3 vWD, higher bleeding score, hemostatic treatment one year before study inclusion, and historically lowest vWF active levels were the independent determinants of vWD self-reported severity.[4] In a cohort study of 221 Caucasian index patients with quantitative vWD and 47 people with vWF levels within the lower normal level (50–70 IU/dL), vWF assays and genetic analyses (gene sequencing and copy number variation), and bioinformatic assessment were done.[5] Differences in mutation patterns were observed in relation to subgroups, mainly the contrast between type 1 vWD (vWF antigen <30 IU/dL) and type 1 vWD (vWF antigen: 30–50 IU/dL). Among the index cases, 77 had type 1 vWD (vWF antigen <30 IU/dL), 111 had type 1 vWD (vWF antigen: 30–50 IU/dL), and 33 had type 3 vWD; mutation rate was 88%, 65%, and 92%, respectively; an overrepresentation of the blood group O was evident in the type 1 vWF antigen: 30–50 IU/dL, mainly among mutation-negative patients, suggesting a potential causal role of blood group.[5]

The physiopathological relationships between vWD and the antiphospholipid syndrome (APS) should merit comments on the present context, due to the described occurrence of a prolongation of activated partial thromboplastin time (APTT) in both clinical conditions.[6–10] Unfolded vWF mediates the binding of platelets without the need for collagen, and β_2-glycoprotein I (β_2-GPI) is a natural inhibitor of the platelet-vWF interaction; the APS is associated with thrombosis, while the main role of auto-antibodies is directed against β_2-GPI.[6] The unfolded vWF levels were comparatively evaluated in 93 normal controls, 64 APS patients, 39 non-APS thrombosis patients, and 49 non-APS autoimmune disease (AID) individuals.[6] The detected levels of vWF were 53% and 50%, respectively, and 36% higher

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in APS patients, non-APS thrombosis patients, and AID patients, in comparison with levels of the normal controls. The APS patients demonstrated high levels of the unfolded vWF in circulation, and auto-antibodies against β_2-GPI may interfere with β_2-GPI-mediated inhibition of vWF-platelet interaction, and the higher unfolded vWF levels in APS might explain associations of APS with thrombosis.[6] The vWF and vWF propeptide profiles were also evaluated in patients with diagnoses of connective tissue diseases (CTD) and APS; primary antiphospholipid antibody syndrome (pAPS) and normal controls were included to better clear the relationships with thromboses.[7] The vWF antigen levels were higher in the patients with CTD and thrombotic thrombocytopenic purpura (TTP), without differences in the vWF levels of CTD with TTP and thrombosis; vWF propeptide levels were significantly high in the patients having CTD with TTP and thrombosis, whereas vWF and vWF propeptide levels were significantly high in the patients with pAPS. These abnormalities in patients with CTD can play a role in the increased risk of thrombosis.[7] The acquired vWS (AvWS) is a rare bleeding disorder with laboratory findings similar to the congenital vWS, and is often associated with lymphoproliferative or cardiovascular diseases.[8] A 42-year-old female was diagnosed with autoimmune AvWS and concomitant APS manifested by episodic epistaxis, besides menorrhagia that started a few years before hospital referral.[8] She presented with marked APTT prolongation, very low levels of vWF ristocetin cofactor activity, and low levels of vWF antigen, besides positive IgG1 and IgG2 anti-vWF antibodies. A vWS remission followed the steroid therapy and re-exacerbated with steroid tapering, while thrombosis did not recur for almost three years after the steroid combination with anti-coagulant.[8] It has been described that severe acute respiratory syndrome coronavirus 2 may induce endothelial chronic oxidative stress, vWF multimer release, and a hypercoagulability status.[9] Many antiphospholipid antibodies (aPL) were observed in cases with COVID-19 acute phase, without confirmation of APS after at least three months, as defined by the laboratory criteria.[9] However, these autoantibodies may cause microthrombotic events and endothelial tissue damage, which may be reactivated in the peripheral nerves and the cerebral microvasculature. The authors highlighted the systematic measurement of vWF and aPL in all individuals hospitalized with COVID-19 to estimate their risk for unfavorable evolution.[9] AvWS and vWD may be suspected based on abnormal bleeding events and family history, but some individuals with mild vWF may evolve with neither hemorrhages nor family history for decades.[10] A 78-year-old hypertensive man with severe aortic stenosis (AS) and no history of hemorrhagic episodes successfully underwent aortic valve replacement surgery, and prolonged APTT was partially improved by massive transfusion of fresh-frozen plasma during the operation.[10] Although a decrease in high molecular weight vWF multimers was not confirmed in this case. AvWS secondary to AS in a patient with aPL was suspected, as aortic valve replacement resulted in an improvement of vWF; ristocetin cofactor and continued mild prolonged APTT.[10] The authors emphasized that the vWF and aPL screening tests must be performed in patients with diagnoses of AS and presenting APTT prolongation in their preoperative evaluations.[10]

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ΠΕΡΙΛΗΨΗ

Νόσος von Willebrand και αντιφωσφολιπιδικό σύνδρομο

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