Von Willebrand factor in polymyalgia rheumatica and giant cell arteritis

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ABSTRACT

Patients with giant cell arteritis (GCA) and with polymyalgia rheumatica (PMR) have increased plasma levels of von Willebrand factor (vWF) even during corticosteroid therapy. The association between vWF, subclinical inflammation and cardiovascular complications in GCA/PMR remains to be investigated.

Von Willebrand factor (vWF) is a high molecular glycoprotein with important function in hemostasis. Diminished function results in von Willebrand's disease, a bleeding disorder. Enhanced activity is involved in the pathogenesis of thrombo-embolic disease. VWF interacts in platelet adhesion and thrombus formation, especially under conditions of high shear stress such as the situation found in small blood vessels. In addition vWF has an indirect function in normal fibrin clot formation as it is a carrier for factor VIII.

Von Willebrand factor is synthesized by endothelial cells and megakaryocytes and is secreted in response to stimuli such as thrombin and fibrin, producing high-molecular weight polymers, and to the permanent secretion of low molecular weight polymers with low activity in the circulation (reviewed by Ruggeri & Ware in ref. 1). Endothelial damage exposes vWF in the sub-endothelial structures, promoting adhesion with the platelet membrane glycoprotein Ib (GPIb). It also binds to GPIIb/IIIa receptors supporting platelet aggregation and thrombus formation (1).

Local secretion of vWF occurs in areas of inflammation and cytokines such as tumor necrosis factor α and interleukin-1 are known to modulate vWF secretion and adhesion *in vitro* (2). It has been speculated that the rapid release of vWF from the secretory granules of vascular endothelial cells and the cell surface expression of P-selectin promote the pathogenic effects of reactive oxygen in atherosclerosis and inflammation (3). The vWF gene is regulated by vascular bed-specific factors derived from the local environment. Thus endothelial cells from different vessels may have distinct functional properties regarding vWF synthesis (4).

Atherosclerosis is recognized as a chronic inflammatory disease (reviewed by Russel, ref. 5). The disease process induces the endothelium to a pro-coagulant state, and plaque rupture and thrombosis are considered to be the most common precipitating events in acute coronary syndromes and myocardial infarction (5). Several of the risk factors for atherosclerosis such as diabetes mellitus, hypertension, hypercholesterolemia, smoking, obesity and high age are associated with high vWF levels in the circulation (6). In epidemiological studies of cardiovascular disease, both coagulation factors and markers for inflammation have been identified as risk factors. A high concentration of vWF predicted reinfarction and mortality in survivors of myocardial infarction (7). In addition to fibrinogen and tissue plasminogen activator (t-PA), vWF has been indicated to be an independent risk factor of myocardial infarction and sudden death in patients with angina pectoris (8). In so far as C-reactive protein (CRP) has been associated with an increased risk for myocardial infarction or sudden death in patients with ischemic heart disease (8), and vWF acts as an acute phase protein, there is a current debate as to whether the association between vWF and cardiovascular disorders may reflect the severity of the disease rather than a true prognostic factor (6).

Elevated levels of vWF in the circulation have been found in systemic inflammatory diseases and vWF has been suggested as a marker of endothelial dysfunction in vasculitis. The plasma levels of vWF are increased in patients with giant cell arteritis (GCA) and in poly-

myalgia rheumatica (PMR) (9-11). Unlike the acute phase proteins, levels of vWF do not decrease with corticosteroid therapy (9-11). Thus, persistently high levels of vWF might reflect a subclinical disease with continued endothelial activation. This hypothesis is consistent with the observation that IL-6 levels remain elevated during corticosteroid therapy despite normalised ESR in a subset of PMR patients (12). Studies have shown that vWF levels remain at high levels for years after the diagnosis of GCA and PMR (11,13). Increased vWF levels in GCA or PMR could reflect an endothelial activation due to stimulation of cytokines released from circulating monocytes (14). Also production of vWF might be due to the angiogenetic activity in the capillaries of vasculitic areas of the arteries in GCA.

Measuring levels of vWF has not been helpful for clinical management or in predicting relapse or the risk for vascular complications in GCA (9). Multiple conditions affect vWF, especially in elderly patients as vWF is associated with atherosclerosis and its risk factors. Glucocorticosteroids increase vWF levels in healthy individuals and also induce plasminogen activator inhibitor-1 (PAI-1) synthesis (15), suggesting an additional hypofibrinolytic factor due to the therapy. In addition, individuals of the ABO blood group O have lower vWF levels compared to those with non-O blood groups (16), a genetic bias that has to be considered when studying patients in small cohorts. In active PMR before corticosteroid therapy, vWF levels correlate with the erythrocyte sedimentation rate and CRP; however, this correlation is mainly restricted to patients with ABO blood group non-O (13). This suggests that the acute-phase response of vWF during inflammation is related to blood group determinants in addition to the proinflammatory cytokines that regulate acute phase proteins. The consequence of continued high levels of vWF in GCA/PMR during therapy is not yet known.

The inflammation in GCA may cause fatal complications due to arteritis, thus a higher mortality in GCA patients may be expected compared to the general population, although most studies have shown a normal life expectancy in patients with GCA (17). Nevertheless, there is an indication for an increased overall mortality in patients with GCA (18), especially in conjunction with cardiovascular disease within the first months after diagnosis (19). In male patients with PMR, decreased survival was associated with cardiovascular disease (20). Our recent findings also indicate that mortality in ischemic heart disease is increased in both men and women with biopsy-proven GCA (unpublished data). Serious acute complications such as visual symptoms or blindness due to vascular occlusion or aortic aneurysms are mostly recognized as complications to GCA. It might be overlooked that myocardial infarction or stroke in a patient with GCA or PMR may be related to the disease and the inflammation.

In conclusion, patients with GCA and PMR have increased plasma levels of vWF for many years. Von Willebrand factor participates in the atherothrombotic process and increased plasma levels of vWF is found in atherosclerosis and in its clinical manifestations. Future research may be focused on the relationship between vWF, the clinical and the cytokine mediated subclinical inflammation and cardiovascular complications in GCA/PMR.

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