Is Acquired Activated Protein C Resistance a Cardiovascular Risk?

To the Editor:

We have read the article by Kiechl et al. demonstrating that acquired activated protein C resistance (APC) may be a risk factor for atherosclerosis and arterial thrombosis in whites. We previously demonstrated that acquired APC resistance is associated not only with venous thrombosis (deep vein thrombosis and pulmonary thromboembolism) but also with arterial thrombosis disease (cerebral infarction and coronary artery disease) in the Japanese population. It is well known that no Japanese has factor V Leiden mutation because of the founder effect of this mutation. Thus, it is likely that in Japanese, some environmental factors might contribute to APC resistance. In addition, we demonstrated a positive association of APC sensitivity ratio with plasma levels of the activated form of factor VII (FVIIa), an activation marker of the early phase of the tissue factor pathway of coagulation in healthy subjects; correlation coefficient $-0.38, P<0.05, n=33$.

More recently, pregnancy-related APC resistance has also been reported to be associated with thrombin-antithrombin complex (an indicator of in vivo thrombin generation) (correlation coefficient with APC sensitivity ratio $-0.274, P=0.01, n=128$). Thus, the APC resistance may reflect the global insensitivity of APC and may provide a good method to assess the hypercoagulable state in vivo. The hypercoagulable state induced by acquired APC resistance should be given greater emphasis in clinical practice in the future.

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Response

Kario et al emphasized the significance of acquired activated protein C (APC) resistance in arterial diseases and established some links to other coagulation abnormalities. This issue is relevant to a better understanding of thrombotic disorders and deserves further comment.

In the Bruneck study, insensitivity to APC not caused by the Leiden mutation emerged as a strong risk predictor of advanced atherosclerosis and arterial disease. This finding was not unexpected given the well-established association between APC resistance and arterial/venous thrombosis in nonwhite populations in which factor V mutations are particularly rare or even absent. Until recently, however, the condition of factor V mutation–independent APC resistance has attracted only minor attention in clinical research. In 1998, Sampram and colleagues were the first to report an increased risk of peripheral artery disease in patients with APC resistance but no gene mutation. The Bruneck study extended these findings to other types of vascular disease and atherosclerosis in general. In the past months, the issue was also settled for venous thrombosis. Two large surveys consistently observed an increased risk of venous thromboembolism among subjects with APC resistance but no factor V Leiden. In the Bruneck cohort, 57 subjects experienced venous thrombosis. APC resistance with and without the factor V mutation was observed in 9% of patients each, and both conditions afforded an increased risk of disease status (OR 3.8 and 3.3, $P<0.05$).

Prevalence of phenotypic APC resistance without detectable gene mutation was underestimated from previous case-control studies. In the Bruneck study, which is representative of the general community in central Europe, this condition was at least as frequent as the Leiden mutation itself. In the population-based Vicenza Thrombophilia Project, the factor V mutation and n-APC ratios $\leq 0.84$, which conferred a significantly increased thrombosis risk, occurred at a ratio of 1:4.

All studies in concert provide substantial evidence of a prominent role of an inadequate protein C pathway in all kinds of thrombotic diseases. The factor V mutation is only one facet of this association. We agree with Kario et al that the time has come to recommend the use of functional APC assays in the risk evaluation of subjects with venous/arterial thrombosis. When doing so, one should be aware of the potential influences that the acute phase reaction evoked by severe illness and infections can have on APC ratios and, if applicable, consider remeasurement at a later date for the purpose of confirmation.

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