

## Inflammatory markers for ischaemic stroke

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Experimental and clinical evidence accumulated since 1990 have established inflammatory processes as important contributors to atherogenesis (1). Based upon this evidence, protein markers of inflammation have been studied as non-invasive indicators of underlying atherosclerosis in apparently healthy individuals and of the risk of cardiovascular events in patients with established atherosclerotic diseases. The most extensively studied biomarker of inflammation in cardiovascular diseases is C-reactive protein (CRP), an acute phase protein that is produced predominantly by hepatocytes under the influence of cytokines such as interleukin (IL)-6 and tumour necrosis factor (TNF)- $\alpha$  (2). Data from more than 30 epidemiologic studies have shown a significant association between elevated serum or plasma concentrations of CRP and the prevalence of underlying atherosclerosis, the risk of recurrent cardiovascular events among patients with established disease, and the incidence of first cardiovascular events among individuals at risk for atherosclerosis (3). Although it is plausible that CRP serum levels are increased as part of the acute phase response to inflammation, experimental evidence has also raised the possibility that CRP is a direct participant in the progression of atherosclerosis and its clinical consequences (4). Indeed, CRP infusion is associated with marked elevations in markers of both inflammation, such as IL-6, IL-8, and serum amyloid A, and coagulation, such as von Willebrand factor (vWF) antigen, prothrombin F1+2, D-dimer, and plasminogen activator inhibitor type 1 (PAI-1) (5).

Regarding cerebrovascular diseases, the data in the literature indicate that CRP is an independent marker for the development and progression of early carotid atherosclerotic disease (6), the risk of ischaemic stroke (7), and the prognosis after stroke (8–10). In addition to CRP, other markers of inflammation are predictors of cardiovascular disease in healthy men and women. In men, plasma IL-6 concentrations have been shown to be predictive of a future myocardial infarction (11). Among patients with unstable or stable angina or even mild angiographic coronary disease, increased serum levels of IL-18 may be an indepen-

dent predictor of cardiovascular mortality (12). One analysis found that circulating serum concentrations of soluble receptors for TNF- $\alpha$  are correlated with coronary risk among women (13). Other studies have found an association between the serum concentrations of soluble intercellular adhesion molecule-1 (sICAM-1) and P-selectin and the future development or exacerbation of cardiovascular diseases (14). Elevated serum concentrations of soluble vascular cell adhesion molecule-1 (sVCAM-1) and E-selectin also may have predictive value (14).

In a study published in the current issue of *Thrombosis and Haemostasis*, Licata and his collaborators add to our knowledge on immuno-inflammatory markers and ischaemic stroke (15). By studying individuals with different subtypes of ischaemic stroke, classified according to the TOAST scheme, they demonstrate that plasma levels of important inflammatory molecules, such as IL-6, TNF- $\alpha$ , and IL-1 $\beta$ , are significantly higher in subjects with stroke of cardio-embolic origin than in subjects with other subtypes of stroke. In addition, they show that, in subjects with stroke, neurological deficit at admission, as measured by the Scandinavian Stroke Scale (SSS), is significantly and independently correlated to IL-6 and TNF- $\alpha$  plasma levels. Licata's findings are important for several reasons. First of all, they demonstrate that different subtypes of ischaemic stroke are associated with different levels of activation of inflammatory markers. Second, the demonstration that increased plasma levels of inflammatory cytokines are particularly evident in cardio-embolic strokes provides support to the hypothesis that inflammation may be associated with atrial fibrillation and contributes to the pathogenesis of arrhythmic disorders (16). Finally, the fact that IL-6 and TNF- $\alpha$  plasma levels correlate with stroke subtype and SSS score suggests that the evaluation of these inflammatory markers might be useful for a better characterisation of subjects suffering from acute ischaemic cerebrovascular diseases. These findings might have important implications for the clinical management of subjects affected by ischaemic cardiovascular diseases.

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