C-Reactive Protein and Cerebral Small-Vessel Disease
An Opportunity to Reassess Small-Vessel Disease Physiopathology?

Mario Di Napoli, MD; Francesca Papa, MD

Stroke places a large burden on healthcare and social services resources in the older adult population. Because the incidence of stroke increases with advancing age, and the population is aging, the number of patients affected by stroke is increasing.

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The burden of stroke goes well beyond those cases that are clinically recognized. Imaging techniques of the brain have revealed a remarkably high prevalence of white matter lesions (WML) and silent brain lacunar infarcts (SBLI). In the National Heart, Lung, and Blood Institute–sponsored Cardiovascular Health Study, SBLI ≥3 mm were found in 31% of all subjects. Fewer than 15% of patients with such lesions had a clinical history of stroke. The prevalence of SBLI increased with advancing age; 22% of subjects 65 to 69 years old had SBLI, as compared with 43% in subjects ≥80 years old. WML involving in particular the centrum ovale are a subject of great interest. Partly this is because modern neuroimaging methods detect subcortical WM changes with increasing frequency in people >60 years old and also because these abnormalities may be associated with specific neurobehavioral deficits, including dementing syndromes. The descriptive term leukoaraiosis (LA), frequently applied to these neuroimaging abnormalities of the WM, refers to bilateral and either patchy or diffuse areas of hypodensity on CT or hyperintensity on T2-weighted MRI.

In this issue of Circulation, van Dijk and colleagues explore the relationship of C-reactive protein (CRP), a well-known systemic marker of inflammation, with the severity and progression of cerebral WML/LA on MRI scans. The investigators examined the prevalence and incidence of brain WML/LA and SBLI in the prospective cohort of 1033 older adult participants of the population-based Rotterdam Scan study. They confirmed a relationship between inflammation and the severity and progression of cerebral WML/LA and SBLI independent of other cardiovascular risk factors and severity of carotid atherosclerosis. The authors suggest that CRP and inflammatory processes could be involved in the pathogenesis of cerebral small-vessel disease (SVD), and in particular in the development of WML/LA. These data raise questions about the relationship between SVD and inflammation. That said, the evolving concept of using a highly sensitive assay for CRP as a marker of SVD risk is enticing, and the message suggested by results of this study is both provocative and in line with the increasing body of literature rapidly accumulating in the exciting field of cerebrovascular disease.

The data of van Dijk et al on the positive correlation between CRP blood levels and SVD appear persuasive; CRP was largely independent of traditional factors and severity of systemic atherosclerosis as assessed by ultrasound carotid examination. The present Dutch cohort is the largest to report on WML/LA and SBLI prevalence as the primary end point. WML/LA severity correlated positively with CRP levels, with a progressive rise in WML/LA severity with CRP level in the top quartile. The difference across groups is impressive: 17% in WML/LA severity and 41% in WML/LA volume progression—the difference between subjects with lowest CRP level and those with CRP level in the top quartile. Furthermore, it is important to bear in mind that the CRP assay was conducted at baseline and that no data are presented on the evolution of CRP over the subsequent 3-year follow-up. The predictive value of CRP level is all the more notable because the strength of the relationship should be underestimated given the expected fluctuation of inflammatory responses.

Evidence continues to mount suggesting important roles for inflammation and genetic factors in the process of atherosclerosis, and specifically in cerebrovascular disease. Our current understanding of the vascular biology of atherogenesis and its clinical manifestations suggests a pathophysiology that is much more complex than mere lipid storage. The weight of evidence supports the current view of atherosclerosis as an inflammatory process that initiates and promotes lesion development to the point of acute thrombotic complications and clinical events. CRP has consistently been observed to be related to the risk of cerebrovascular and cardiovascular events and is consistently elevated in the circulation of patients after acute ischemic stroke, even when factors known to be associated with raised CRP concentrations such as infection and atherosclerosis are taken into account. Several prospective studies indicate that elevated CRP concentration increases the risk of cerebrovascular disease, independent of conventional risk factors (Figure 1); however, most evidence hitherto has involved atherothrombotic stroke. The CRP–cerebrovascular disease relationship is opening intriguing avenues for research, screening, and prevention. Not surprisingly, the study by van Dijk et al raises...
more questions than answers. We should search for the origin of this acute-phase response; so far, no hypothesis on the source of inflammation has been proven. We should search for the reasons for a strong association between inflammatory status and WML/LA progression. The answer to these questions lies at many levels and ultimately may point to the futility of our present approach to complex disorders. These observations underscore the multifactorial pathogenesis of cerebrovascular disease and the complementarity of multiple factors for prediction of risk or as targets for therapeutic intervention. A complex interplay between proinflammatory stimuli and endogenous heritable-genetic vascular reparative processes should be considered as a determinant of vascular disease activity.

The mechanisms underlying SVD are incompletely understood. It should be remembered that there are a large number of potential causes of small-vessel occlusion, most of which have been postulated or proven at some time as a rare cause of SBLIs. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy has been shown to be caused by highly stereotyped mutations in the Notch3 gene, a large transmembrane receptor involved in cell fate decisions during embryogenesis and promotion of vascular smooth muscle cell survival but a rare condition in patients with cerebral SVD. This heterogeneity of SVD applies not only to the underlying vessel lesions but also to brain lesions; there is, for example, both pathological and clinical evidence that small infarcts in the centrum ovale, probably lying in subcortical territories, are more commonly the poststenotic hypothesis that results from disease in the small perforating arteries that disrupt flow at the origin of the perforating arteries. SBLI may be one of the reasons the blood supply to the WM is altered, and this vascular alteration may lead to either localized ischemic areas of necrosis and cavitation (ie, SBLI) or diffuse rarefaction (ie, WML/LA). Small-vessel atherosclerosis is also casually implicated in a proportion of SBLI.

The most common risk factor for WML/LA is aging; arterial hypertension, diabetes mellitus, and cardiac diseases are additional risk factors frequently associated with WML/LA. Aging, chronic hypertension, and diabetes share a common substrate in the type of alterations that these conditions induce on the small penetrating arteries and arterioles of the WM. Such changes include replacement of the smooth muscle cells by fibrohyaline material with thickening of the wall and narrowing of the vascular lumen (arteriosclerosis). The most popular hypothesis is that this results in an inability of the blood vessels to maintain and autoregulate cerebral blood flow and therefore predisposes to ischemia. Arteriosclerosis, almost always detected within areas of WML/LA, may be one of the reasons the blood supply to the WM is altered, and this vascular alteration may lead to either localized ischemic areas of necrosis and cavitation (ie, SBLI) or diffuse rarefaction (ie, WML/LA). Small-vessel atherosclerosis is also casually implicated in a proportion of SBLI.

Although modern concepts of atherosclerotic plaque biology and natural history have yet to be applied to small cerebral vessels, plaque ulceration/rupture is not typical of intracranial arterial occlusion. Although atherosclerotic lesions in different vascular beds share many characteristics, mechanisms related to symptomatic conversion likely are site specific. The mechanism of infarction was related either to occlusive thrombosis (perhaps exacerbated by the hypercoagulable state associated with essential hypertension) or to a nonocclusive poststenotic hypoperfusion. This view is supported by the distribution of frequently associated chronic ischemic changes, seen radiologically as WML/LA. Such lesions start first in the regions of the WM furthest from the origin of the perforating arteries, which are those most likely to suffer from hypoperfusion. It is also possible that microatheroma in the basal intracerebral vessels plays a role in SVD by disrupting flow at the origin of the perforating arteries. SBLI results from disease in the small perforating arteries that supply the deep WM, basal ganglia, and brain stem structures. These are end arteries with no collateral supply; therefore,
disruption in their blood supply results in a small discrete region of infarction, referred to as an SBLI.

The specific risk factor profiles of SVD are still being developed but are broadly similar to the risk factor profile of large-vessel ischemic stroke, differing mainly in terms of emphasis of individual factors. Although hypertension has traditionally been regarded as the cardinal risk factor for SVD, this association is likely to have been overemphasized in the past. A significant proportion of patients with SVD appear to always have been normotensive.14 Nevertheless, complex alterations in blood pressure regulation may contribute to the pathogenesis of WML/LA. Compared with matched control subjects, people with WML/LA have both high blood pressure values and a different circadian rhythm that is characterized by either a lack of the nocturnal physiological drops in blood pressure or wide daily fluctuations and is consistent with the demonstration of impaired cerebral autoregulation in hypertensive patients who have severe periventricular WML/LA.15 Furthermore, in a novel inbred rat model of inducible hypertension, in which the degree and duration of hypertension are tightly regulated in a dose-dependent and reversible manner, there is indeed differential susceptibility of organs to the hypertensive stimulus, mediated perhaps by the local renin-angiotensin system.16 In this model, the brain appears to be, paradoxically perhaps, relatively resistant to vascular injury compared with heart, mesentery, and kidney. Clearly, much remains to be learned about the hierarchy of susceptibility of different vascular beds to hypertension, but these new models of hypertension offer novel experimental insights. To this end, various lines of evidence implicate disordered small-vessel tone in SBLI in particular. The new generation of hypertensive laboratory animals have the potential to further our insight; for example, normotensive rats transgenic for the prorenin gene develop classical hypertensive end-organ damage, including fibrinoid necrosis.17 The significance of this observation is that fibrinoid necrosis can be dissociated from raised blood pressure and damage is thought to be mediated by local generation of angiotensin II (Ang II), which is both a potent vasoconstrictor and influences cell growth and matrix deposition, which are important in vascular wall remodeling.18 Evidence from numerous sources suggests that the powerful endogenous vasoconstrictors Ang II19 and endothelin-120 may act as a proinflammatory stimulus in addition to their vasoconstrictor effects. The actions of Ang II are mediated in large measure by stimulation of production of superoxide anion (O₂⁻) and activation of redox-sensitive genes.21 Some of these include genes participating in inflammatory responses to Ang stimulation. Among these are nuclear factor κB (NF-κB) and transcription factor AP-1, associated with the upregulation of adhesion molecules such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, and stimulation of the production of chemokines such as monocyte chemotactic protein-1 followed by recruitment of monocytes/macrophages to the vascular wall. The induction of the inflammatory response is regulated by the transcription of NF-κB mediating most of the vascular inflammatory responses.22 A major pathway leading to NF-κB activation involves phosphorylation of NF-κB inhibitor (I-κB), a transcription factor involved in the expression of the genes encoding many proinflammatory functions of vascular wall cells and infiltrating leukocytes, by I-κB kinase. Although I-κB kinase is a key regulator of the NF-κB pathway, ubiquitination of I-κB and its subsequent degradation by the proteasome are also required for NF-κB activation.23 After activation, NF-κB translocates into the nucleus, where it regulates the transcription of genes involved in the pathogenesis of inflammatory lesions. Indeed, these genes encode for cytokines such as interleukin-6 and tumor necrosis factor-α, chemokines such as monocyte chemotactic protein-1, and intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and platelet endothelial cell adhesion molecule; all are involved in the recruitment of monocytes/macrophages to sites of inflammation in the vascular wall (Figure 2).24

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**Figure 2.** Central role of inflammation as a determinant of biology underlying acute thrombotic complications of atherosclerosis. Current complex understanding of the interrelationship between inflammation and thrombogenicity depicted. Adapted with permission from Di Napoli and Papa.24
Endothelial dysfunction has also been proposed as a causal mechanism of SVD. When endothelium is damaged or becomes dysfunctional, a cascade leading to atherogenesis is precipitated, initiating a cycle of injury, immunologic induction, and amplification. Causes of endothelial dysfunction include arterial hypertension, smoking, diabetes, exposure to high levels of oxidized low-density lipoprotein, homocysteine, and fibrinogen. This may result in part from decreased production of nitric oxide (NO). Also, augmented release of O_2 may annihilate NO radical, neutralizing its vasodilator capacity. In addition to producing vasodilatation, NO can impair platelet aggregation. NO also has a direct antiinflammatory effect, suppressing production of NF-κB. Dysfunctional endothelium leads to increased permeability to lipoproteins, impairs cerebral autoregulation, and promotes a prothrombotic state. Upregulation of leukocyte and endothelial adhesion molecules can lead to breakdown of the blood-brain barrier. These various findings highlight the central role of inflammation into the physiopathology of SVD. Perhaps it is not coincidental that NO and Ang II have been 2 of the mediators of vessel tone linked experimentally to fibrinoid necrosis. Provisional genetic polymorphism studies have identified a weak but significant association between the angiotensin-converting enzyme gene and endothelial NO synthase gene polymorphism with SVD. There are therefore genetic markers emerging from individuals who are at risk of developing SVD, offering the possibilities of specific and targeted preventive treatment.

These new data regarding the possible effects of inflammatory reactions in SVD may be of more than just academic interest. Inflammatory reactions may play a crucial role in both the initiation and progression of SVD. Despite these advances in our understanding of SVD physiopathology, much remains to be done. Additional inroads may well emerge as we begin to apply our recently acquired knowledge of the role that inflammation plays in cerebrovascular disease. In all likelihood, future basic research, including the application of functional genomics, will teach us new lessons about atherothrombosis and its complications and show the path to additional ways to limit this disease. In the coming years, we will see delineation of polymorphisms in the human genome, some of which will doubtless predict an individual’s cerebrovascular risk. We believe that we will target our preventive therapies by a combination of a panel of new serum tests, including some traditional and a few nontraditional markers. These markers will provide an integrated assessment of the interaction between genotype and the environment, including individual behaviors (eg, smoking, diet). Genotyping, probably accomplished by high-throughput screening early in life, will identify genetic markers (eg, single nucleotide polymorphisms, haplotypes) that should predict individual responses to risk factors. The combination of the serum markers and hereditary predisposition revealed by genetic analysis should sharpen our ability to prescribe risk management in individuals in a rational manner. It may be that adding evaluation of inflammatory markers to conventional risk factors not only will allow intervention to be targeted to more appropriate patients but also will define which specific drugs an individual should receive.

**References**


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