Hemostasis and Vascular Dementia

Philip M.W. Bath, Peter R. Anderton, Sandeep Ankolekar

Vascular dementia (VaD) comprises a group of syndromes caused by vascular lesions in the brain. Cognitive impairment may follow a single cortical or lacunar infarct in a strategic area of the brain, multiple infarcts, small-vessel disease (leukoaraiosis), intracerebral hemorrhage, or any of these conditions coexisting with Alzheimer dementia (so-called mixed dementia). Depending on case mix and the type of observational study, 10% of patients already have dementia before their first stroke, 10% develop it soon after their first stroke, and more than 33% have dementia after a recurrent stroke. Typically, dementia develops at a rate of 3% per year after stroke, and it is the stroke, rather than its underlying risk factors, that appears to be the dominant cause of subsequent dementia.

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Although VaD, including poststroke dementia, is associated with conventional risk factors, such as hypertension and hypercholesterolemia, their relationship with hemostatic factors is less clear. This contrasts with the relationship between hemostatic factors and stroke, which is well established and involves both soluble (e.g., fibrinogen) and cellular (e.g., mean platelet volume) biomarkers. Several hemostatic factors, including fibrinogen and fibrin D-dimer levels, are associated with subsequent cognitive impairment and dementia in observational studies (Table). This issue of Arteriosclerosis, Thrombosis, and Vascular Biology expands on this relationship between “sticky blood” and cognition. Two new studies are described.

First, Stott and colleagues report observational data from the PROSpective Study of Pravastatin in the Elderly at Risk (PROSPER), which examined lipid lowering in 5699 people (average age, 75 years) not taking warfarin had measurements of hemostatic factors at baseline and annual assessments of cognition over 3.2 years of follow-up. Cognitive measures included speed of information processing (Letter Digit Coding Test and Stroop test) and verbal memory (picture-word naming). The central finding was that increased levels of D-dimer and prothrombin fragment 1+2 (ie, markers of thrombin generation) were associated independently with cognitive decline and deterioration in activities of daily living (Table). Interestingly, markers of endothelial dysfunction (eg, tissue plasminogen activator and von Willebrand factor) were not associated with cognitive decline.

Second, Gallacher and colleagues present data on 865 men free of vascular disease, with biomarker measurements, who were observed in the Caerphilly community cohort. Hemostasis factors were measured at the age of 45 to 59 years, and cognition and dementia were determined up to the age of 65 to 84 years. During 17 years of follow-up, 59 of the men developed dementia and 112 developed cognitive impairment/no dementia. Increased fibrinogen, factor VIII, and plasminogen activator inhibitor-1 levels were associated independently with VaD (Table). In contrast, increased levels of these factors were not related to non-VaD; however, there were few cases of this occurrence. By using factor analysis and structural equation modeling, VaD appeared to be related to certain coagulation “pathways,” in particular accentuated clot formation (increased fibrinogen and/or D-dimer level), platelet and fibrin plug formation (factor VIII/von Willebrand factor), and possibly impaired fibrinolytic activity (plasminogen activator inhibitor 1); in contrast, increased thrombin generation (thrombin-antithrombin complex and prothrombin fragment 1+2) did not appear to be relevant.

Accepting that their data need confirmation, both sets of these authors (with 1 common member, Gordon Lowe) hypothesize that clot formation contributes to the formation of VaD, ie, the brain undergoes microinfarction. The emphasis on markers of clot formation appears to be a common finding in other longitudinal studies, as summarized in the Table. This mechanism might explain certain types of subcortical dementia (eg, dementia that is possibly related to leukoaraiosis, a condition in which cognitive impairment declines gradually). However, subcortical dementia secondary to frank lacunar infarction, and cortical dementia related to large-artery disease or cardiac embolism, may be of rapid or stepwise onset if macroinfarction occurs in strategic areas, leading to disruption of cortical-subcortical circuits and cortical deactivation. Microinfarction also cannot explain dementia following intracerebral hemorrhage unless leukoaraiosis is also present. Clearly, future studies of the relationship between hemostasis and VaD need to include adequate phenotyping using computer tomographic or, ideally, magnetic resonance scanning to quantify stroke lesions, leukoaraiosis, and atrophy.

The relationship between hemostatic factors and different types of dementia remains unclear. Although both Gallacher and Carcaillon, and their colleagues, did not find a relationship with non-VaD, others have found positive associations between incident Alzheimer dementia and fibrinogen; however, the relationship was less strong than for VaD. One potential explanation is that the presence of Alzheimer dementia within mixed dementia may dilute the relationship between hemostatic factors and pure VaD.
Some cross-sectional and longitudinal studies have suggested that markers of inflammation (including C-reactive protein, interleukin 6, and vascular cellular adhesion molecule-1) are also associated with cognitive impairment and dementia. Therefore, it is of interest that no such relationships were seen in the Caerphilly cohort, a finding present in some other studies. Nevertheless, the close interaction between inflammatory and thrombotic pathways requires that further studies address the role of both in promoting cognitive impairment.

If at least some cognitive impairment follows microinfarction secondary to a prothrombotic state, the next question is how can it be delayed or prevented therapeutically. Oral anticoagulation with warfarin might be attractive because it reduces prothrombin fragment 1 + 2, thrombin-antithrombin complexes, and D-dimer; safety concerns exist about its use in patients with leukoaraiosis (ie, the group in whom it is present in some other studies). Nevertheless, the close interaction between inflammatory and thrombotic pathways requires that further studies address the role of both in promoting cognitive impairment.

Antiplaletlets offer an alternative approach to reducing microinfarction and macroinfarction. However, there is no conclusive evidence that aspirin reduces cognitive decline; different antiplatelet strategies (aspirin and dipyridamole versus clopidogrel) did not differ in their effects on cognition or dementia. Whether antithrombotic agents promote intracerebral bleeding in people with microbleeds, another potential risk factor for dementia, also remains unclear. Such uncertainties demand further clinical trials to remove current clinical equipoise. The Secondary Prevention of Small Subcortical Strokes (SPS) 3 trial is assessing, in a factorial design, whether clopidogrel should be added to aspirin, and whether blood pressure should be lowered intensively, in patients with lacunar infarction. Although stroke recurrence is the primary outcome, cognitive function is also being studied prospectively (data available at: clinicaltrials.gov/ct/show/NCT00059306; downloaded November 27, 2009). In contrast, cognitive impairment and dementia are the primary outcome in the Prevention Of Decline in Cognition After Stroke (PODCAST) trial, a factorial study of intensive versus guideline blood pressure and lipid lowering (available at: http://www.controlled-trials.com/ISRCTN85562386;/ downloaded November 27, 2009). These latter interventions are relevant because statins and most antihypertensive agents are pleiotropic and have mild antithrombotic activity.

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