EDITORIAL

Is sticky blood a treatable determinant of cognitive decline and of dementia?

The traditional saying ‘a man is as old as his arteries’ implies that vascular factors play a role in dementia, and there is increasing evidence for this hypothesis from epidemiological studies.

Such evidence has recently been reviewed by investigators in the Dutch Study on Vascular Factors in Dementia, which was based on the Rotterdam population study and the Rotterdam Stroke Data bank [1]. Classical risk factors for vascular disease, as well as markers of atherosclerosis, appear to increase the risk for dementia (including both its vascular and Alzheimer’s subgroups). Recently described possible associations of dementia include the apolipoprotein E genotype, the factor V Leiden mutation (which increases risk of venous thrombosis), and markers of activated coagulation and fibrinolysis.

These latter findings suggest the possibility that lipids and thrombosis may play a role in dementia; possibly by effects not only on large vessel athero-thrombo-embolism, but also on cerebral small vessel disease [1]. The possibility that antithrombotic therapy (e.g. with aspirin or warfarin) might have a beneficial effect on the occurrence and the progression of decline in cognitive function, and on progression of dementia [2, 3] is currently being tested in randomized controlled trials.

Studies of the flow resistance of blood (rheology) have suggested that viscosity (the intrinsic flow resistance of whole blood or plasma) may be an important determinant of cerebral blood flow, especially in elderly subjects and in the presence of acute stroke or acute confusional states [4–7].

Randomized trials of aggressive reduction in blood viscosity by haemodilution (which also reduces blood oxygen transport to the brain) or defibrinogenation with the snake venom enzyme, anecrod (which also increases the risk of intracranial haemorrhage), have not supported their use in patients with acute stroke [7, 8].

On the other hand, simple rehydration in patients with acute stroke or acute confusional states lowers blood viscosity, and this simple, traditional component of good medical and nursing care in general medical, care of the elderly and stroke wards may thus have a plausible pathophysiological basis for improving recovery by improving cognitive function, reducing the volume of cerebral infarction (major and minor), and reducing the risk of venous thrombo-embolism.

Blood viscosity and cognitive decline

If keeping blood viscosity within the low-normal range and maintaining brain performance by rehydration is beneficial to the acutely-challenged, hypo-perfused brain in older patients, can we extend the potential link between blood viscosity and brain function to chronic cognitive decline in the general population?

Blood viscosity and its major determinants (haematocrit, plasma viscosity and red cell aggregation as measured by the erythrocyte sedimentation rate) appear independent determinants of the risk of coronary heart disease [9, 10], and there is some evidence that blood viscosity, haematocrit, plasma viscosity and plasma fibrinogen (an important determinant of plasma viscosity and red cell aggregation) also increase the risk of stroke [11]. The latter effect may be partly due to an effect of blood viscosity on carotid artery atherogenesis [12], but may also reflect an effect of viscosity on cerebral blood flow at microvascular level. Such an effect may also be relevant to risks of cognitive decline and dementia.

In this issue of Age and Ageing, Elwood and colleagues [13] report the first epidemiological study of the relationship between cognitive function and blood rheology, from the Caerphilly cohort study of older men in the UK. This ‘British Framingham’ study is unique in developing the classical ‘town cohort’ concept of Framingham to include both new prospective risk factors and new measures of cardiovascular disease, including cognitive function as a risk marker for dementia.

The report has two messages. First, the best cognitive function scores occurred at a mean haematocrit of 0.46 (which is the mean haematocrit for men in the UK and in other developed countries), with lower scores
at haematocrit extremes. This finding supports the long-standing practice concept that treatment of both anaemia (haematocrit under 40 in men) and polycythaemia (haematocrit over 52 in men) is appropriate for both general health and brain health. Secondly, there was a strong inverse relationship between cognitive function and plasma viscosity, which was not explained by plasma fibrinogen. This finding begs the questions: what plasma components might explain the inverse association between plasma viscosity and cognitive function, and can such components be modified?

Lipoproteins and viscosity

Recent studies suggest that this 'missing link' could be lipoproteins. Next to fibrinogen, lipoproteins have the strongest effects on plasma and blood viscosity in both experimental and epidemiological studies [10].

In a recent report from a large randomized placebo-controlled trial of primary prevention of coronary heart disease with pravastatin (the West of Scotland Coronary Prevention Study), lipoprotein reduction with pravastatin reduced plasma and blood viscosity (by about one-quarter of a standard deviation) [10]. Two recent studies have suggested that statins are associated with a substantial decreased risk of dementia [14, 15] and, together with the report of Elwood et al. [13], the evidence from all these studies supports the hypothesis that statins may reduce the risks of cognitive decline and dementia by reducing plasma lipoproteins and hence plasma and blood viscosity, thus improving cerebral perfusion and hence maintaining brain function.

In the ongoing PROSPER study of men and women aged 70–82 years in Glasgow, we are testing the hypothesis that pravastatin reduces the risk of major cardiovascular events including stroke. We are also prospectively testing the hypothesis that pravastatin reduces decline in cognitive function (a tertiary outcome measure), and that changes in cognitive function are related to changes in plasma viscosity in both pravastatin and placebo-treated groups.

We should not ignore the effects of the menopause and hormone replacement therapy (HRT) on cognitive decline in women. HRT reduces plasma viscosity partly through effects on lipoproteins and fibrinogen [16, 17], and may also reduce the risk of dementia [18]. Large studies of HRT use in women should consider measurement of cognitive function, plasma viscosity and its determinants (plasma lipids/lipoproteins, fibrinogen) to address this hypothesis.

In conclusion, there is increasing evidence that we should modify our historical saw: 'a man (or a woman) is as old as their brain perfusion, which is determined not only by their blood vessels, but also by the ability to control the flow of the blood passing through them, which may be easier to modify.' This is a testable hypothesis.

References

