Haemorheological predictors of cognitive decline: the Edinburgh Artery Study

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Abstract

Introduction: vascular risk factors and diseases can negatively impact cognitive function. Determinants of blood flow are implicated in thrombogenesis and ischaemic events, yet little is known about their relationship with cognition.

Methods: blood rheology data were collected in 1987/88, and cognitive testing was performed in 1998/99 when the mean (±standard deviation) age of the study sample was 73.1 years (±5.0). Follow-up assessment was performed 4 years later. Information was collected on verbal declarative memory, non-verbal reasoning, verbal fluency, information processing speed and a general cognitive factor representing the variance common to the individual test scores.

Results: after controlling for age, sex and cognitive performance in 1998/99, blood viscosity (BV) (P<0.05) and fibrinogen (P<0.05) predicted decline in non-verbal reasoning over 4 years. When estimated from pre-morbid level, decline in general cognition (P<0.05), non-verbal reasoning (P<0.05) and information processing speed (P<0.01) was associated with BV levels. Haematocrit (HCT) had similar effects (P<0.01 to P<0.001). All associations persisted after control for multiple confounders. When examined together, HCT but not BV independently predicted cognitive decline.

Conclusions: blood rheology is independently related to cognitive decline in older people. The value of strategies aimed at preserving cognition through influencing blood rheology needs investigation.

Keywords: haemorheology, blood viscosity, haematocrit, cognition, aged, elderly

Introduction

Cognitive impairment is associated with reduced quality of life and survival in older people [1]. Individual differences in cognitive decline are partly attributed to differences in cardiovascular (CVD) risk factors, including smoking, hypertension, diabetes and vascular diseases [2, 3]. In a cohort study [4] of older men and women, stroke was associated with worse verbal memory performance and increased cognitive decline. Stroke-free vascular patients also declined faster in verbal memory. In these patients, asymptomatic thromboembolic events [5–7] and cerebral hypoperfusion [8] may be important pathophysiological mechanisms of cognitive impairment.

Determinants of blood flow have been implicated in atherogenesis, thrombogenesis and the onset of ischaemic events [9]. Compared to studies of established CVD risk factors and vascular diseases, few reports exist on cognitive function in relation to markers of blood rheology (the flow resistance of blood). Whole blood viscosity (BV) and its main components [haematocrit (HCT) and plasma viscosity (PV)] correlate with the degree of carotid intima-media thickness in men [10]. Whole BV and HCT also predict the risk of stroke [11]. Importantly, these associations may be at least as strong as those for established CVD risk factors, including blood lipids, smoking and high blood pressure. Perturbations in blood flow correlate adversely with measured quality of intracranial and extracranial arterial blood flow in older people [12]. Given that adequate cerebral blood flow is intrinsic to intact cerebral function, it is possible that age-associated, long-term alterations in blood rheology may interfere with normal cognitive function [12–15].

The present study aimed to investigate the relationship between markers of blood rheology and change in cognitive function in older people. We specifically (i) determined the relationship between rheological markers measured in 1987/
88 and cognitive change over a 4-year period (1998/99 to 2002/03), (ii) determined the association between these markers and cognitive change from an estimated pre-morbid level to that actually measured in 2002/03 and (iii) examined whether these associations existed independently of major confounding factors.

Methods

Study population
In 1987/88, the Edinburgh Artery Study recruited a random sample of 809 men and 783 women aged 55–74 years. The study population was selected from registers of 11 general practices in Edinburgh [16]. The response rate was 65%, and responders were reasonably representative of the target population.

A clinical examination was conducted in 1987/88 [16]. A questionnaire on sociodemographic [17], medical [18] and lifestyle characteristics was administered. Fasting blood was drawn for analysis of biomarkers. A 12-lead electrocardiograph (ECG) and rhythm strip were recorded and coded using the 'Minnesota Code' [19]. Subjects were asked about a doctor's diagnosis of diabetes and medication use. Information on CVDs was collected in 1987/88, at 5- and 12-year follow-up examinations and through continuous follow-up [16, 20].

Cognitive testing was performed in 1998/99 and subsequently 4 years later (please see the figure in Appendix 1 Age and Ageing online). A health ethics committee granted ethical approval. During 1987/88 to 1998/99, 380 subjects died. One thousand two hundred nine subjects were available for cognitive testing: 1,103 subjects were invited, 61 withdrew, 19 others died and 28 were excluded by their general practitioner (GP). In total, 717 (59.3%) subjects were cognitively tested. By mid-year 2002, 601 (83.8%) of the 717 subjects were still alive, and of these, 23 were excluded by their GP. Four more subjects could not be located. Therefore, 574 (95.5%) subjects were found eligible and were sent an invitation to attend follow-up cognitive testing. Of these, 101 refused participation and 13 failed to reply. In total, 460 of the 574 (76.5%) subjects accepted the invitation and were given an appointment. However, a further seven participants withdrew from the study and one could not be contacted. As a result, 452 subjects (75.2%) were cognitively tested: 280 at a study clinic and 172 at home.

Assessment of rheological factors
As previously described [21], whole BV and PV were measured in ethylenediaminetetraacetic acid (EDTA)-anticoagulated blood at high shear rates (over 300/s) in a Coulter–Harkness viscometer at 37°C. HCT was determined using a Hawksley microcentrifuge and reader. BV was further corrected to a standard HCT of 45%. Relative BV (HCT corrected BV/PV) was also computed as a measure of red cell deformability. Lastly, fibrinogen was assessed by a thrombin-clotting turbidometric method in a centrifugal analyser.

Assessment of cognitive function
The following cognitive tests were administered: (i) the Wechsler Logical Memory Test (LMT) assesses verbal declarative memory [22]. Immediate and delayed recall was assessed, and the combined score was used; (ii) the Raven's Standard Progressive Matrices (SPM) assesses non-verbal reasoning [23]. One point was given for each correctly completed pattern problem; (iii) a phonemic Verbal Fluency Test (VFT) assesses executive/frontal lobe functioning [24]. Three 1-min word-naming trials were used whereby subjects were asked to name as many words as they could think of beginning with the letters C, F and L; (iv) the Wechsler Digit Symbol Test (DST) assesses processing speed [25]. Subjects were asked to complete as many number–symbol pairs as possible in 90s.

Potential confounders
After reviewing the available literature, the following were considered as possible confounding factors: (i) age; (ii) sex; (iii) depression symptoms assessed using the Hospital Anxiety and Depression Scale [26]; (iv) pre-morbid cognition, which on one hand was based on test performance in 1998/99, and on the other, estimated in 2002/03 using the National Adult Reading Test (NART) [27]; (v) pack-years of smoking in 1987/88 [28]; (vi) alcohol intake in 1987/88; (vii) CVD meeting study criteria [16, 20] from 1987/88 to a cut-off date approximately 6 months prior to cognitive testing in 2002/03; (viii) diabetes in 1987/88 was based on subject's recall of a doctor's diagnosis of diabetes, current treatment or 2-h blood glucose concentration.

Statistical analysis
A general cognitive factor (GCF), representing the variance common to all the cognitive tests, was computed by subjecting the LMT, SPM, VFT and DST to a principal components analysis. Scores were saved on the first unrotated principal component. Each cognitive test loaded strongly on this component which accounted for 57.1% of the total variance, thus validating the use of a general factor.

Confounding factors were controlled in three cumulative steps in the multiple regression analysis. Firstly, age and sex were controlled. Then, in subsequent steps, two different types of control were made for pre-morbid ability: (i) the 1998/99 score for the respective dependent cognitive test in 2002/03 was controlled for. The adjustment for 1998/99 test performance on the same test battery allowed the determination of the amount of actual change in specific cognitive functions in relation to rheological markers over
a time frame of 4 years. Using regression in this way, i.e. controlling for prior scores, is superior to using simple change scores [29] since it obviates the spurious correlation between baseline and change scores; (ii) pre-morbid level (based on the NART) was controlled for. By controlling for a well-validated estimate pre-morbid ability, the impact of blood rheology on the imputed decline from best-ever cognitive level was assessed [30]. Finally, depression symptoms, lifestyle and medical factors were controlled for. All tests were two-tailed, and a two-sided probability value (P value) of <0.05 was taken to indicate statistical significance. All analyses were performed using SPSS 14.0 for Windows [31].

Results

Cognitively tested subjects were younger in 1987/88 (62.6 versus 64.0 years, respectively) and healthier as reflected in fewer smoking pack-years (2.7 versus 10.0), lower blood pressure (138.8 versus 144.5 mm Hg) and less CVD morbidity (myocardial infarction (MI) = 2.0 versus 2.2%; stroke = 1.3 versus 2.2%) (please see the table in Appendix 2 in Age and Aging online).

Four hundred fifty-two subjects were tested in 2002/03; 441 had complete data on the LMT in 1998/99 and 2002/03, 427 on the SPM, 442 on the VFT and 407 on the DST. Apart from the LMT (mean difference = 1.48, 95% confidence interval (CI)=0.42–2.54, P < 0.01), all cognitive scores declined between 1998/99 and 2002/03 (SPM: mean difference=−2.18, 95% CI=−2.19 to −3.43, P<0.001; VFT: mean difference=−1.80, 95% CI=−1.08 to −2.52, P<0.001; DST: mean difference=−4.84, 95% CI=−4.25 to −5.43, P<0.001).

Most rheological markers were correlated, with effect sizes ranging from small to moderate. HCT, PV and fibrinogen were correlated with BV (r=0.65, P<0.01; r=0.44, P<0.01; and r=0.19, P<0.01, respectively). PV and HCT were moderately correlated (r=0.16, P<0.01). Fibrinogen was correlated with PV (r=0.36, P<0.01) but not HCT (r=0.01, P>0.05).

After controlling for age, BV correlated with lower scores on the GCF (P<0.01) and all individual cognitive tests (P<0.05 to P<0.01), apart from the VFT (Table 1). HCT correlated negatively with GCF and DST (both P<0.01). PV correlated negatively with GCF (P<0.05) and the SPM (P<0.05) and DST (P<0.01), respectively. Fibrinogen was related to lower GCF (P<0.01), SPM (P<0.05), VFT (P<0.05) and DST (P<0.01) scores, respectively.

The relationship between rheology and cognition was further assessed in a series of regression analyses. Only the main effects are reported because there was no evidence of gender by marker interaction in cognitive function (data not shown). Specifically, after the above associations were additionally controlled for sex, identical results were observed although fibrinogen was no longer associated with performance on the SPM (Tables 2 and 3). When the 1998/99 score on each test was controlled for, BV was only associated with decline on the SPM (P < 0.05) (Table 2), as did fibrinogen (P<0.05). After further controlling for mood and medical confounders, only BV (P<0.05) was associated with decline in SPM scores. Also, pre-morbid cognition, as indexed by the NART, was positively correlated with all cognitive tests (data not shown). All rheology markers correlated with the NART (data not shown). After controlling for the NART, BV predicted decline on the GCF (P<0.05), SPM (P<0.05) and DST (P<0.01), respectively (Table 3). The same pattern was seen for HCT (P ranging from <0.01 to <0.001). No effects of PV were longer observed. Controlling for additional confounding factors did not change the results.

We repeated these analyses for both corrected and relative BV (data not shown). Both markers predicted decline (both P<0.05) in SPM performance after controlling for 1998/99 SPM scores and other confounding factors. Finally, since BV and HCT were highly correlated (r=0.65, P<0.01), we tested their independent cognitive effects by analysing them together while controlling for age, sex and NART scores (data not shown). Only HCT was related to GCF scores (P<0.05). The association persisted (P<0.05) after we controlled for depression, CVD risk factors and disease.

Discussion

This study showed that BV and fibrinogen were associated with a greater decline in non-verbal reasoning in older people. When estimated from a pre-morbid cognitive level, decline in general cognitive function, non-verbal reasoning and information processing speed was also associated with BV levels. HCT was also associated with decline in these same cognitive functions. After correction to a standard HCT, BV was associated with a steeper decline in non-verbal
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Table 2. Multivariate associations between rheological markers in 1987/88 and 4-year change in cognitive performance over 1998/99 to 2002/03

<table>
<thead>
<tr>
<th>Rheological marker</th>
<th>General factor</th>
<th>Logical memory</th>
<th>Raven’s matrices</th>
<th>Verbal fluency</th>
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<td>Blood viscosity (mPa. s)</td>
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<tr>
<td>Age and sex adjusted</td>
<td>−0.34 (0.09)***</td>
<td>−3.14 (1.58)*</td>
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<td>−0.45 (1.29)</td>
<td>−4.17 (1.08)***</td>
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<tr>
<td>Age, sex and NARTa adjusted</td>
<td>−0.20 (0.08)*</td>
<td>−1.93 (1.55)</td>
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<tr>
<td>Fully adjustedb</td>
<td>−0.17 (0.08)*</td>
<td>−1.89 (1.63)</td>
<td>−2.14 (0.89)*</td>
<td>1.20 (1.25)</td>
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<td>Haematocrit (%)</td>
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Further adjusted for depression symptoms in 2002/03, pack-years of smoking, alcohol consumption, diabetes/glucose intolerance, all at baseline in 1987/88, and any major cardiovascular disease from baseline up to 6 months prior to cognitive testing in 2002/03.

The Caerphilly studied general cognitive function and choice reaction time in relation to PV, HCT and fibrinogen [13]. PV was associated with both cognitive outcomes after adjustment for age and social class. We did not find a rela-

reasoning. This was also observed for relative BV, an indicator of red cell deformability. When examined together, HCT rather than BV was found to predict decline in general cognitive function.

Table 3. Multivariate associations between rheological markers at baseline in 1987/88 and cognitive change from estimated pre-morbid cognitive level

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P<0.05.

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Best-ever or pre-morbid cognitive ability was estimated from performance on the National Adult Reading Test (NART) in 2002/03.

Further adjusted for depression symptoms in 2002/03, pack-years of smoking, alcohol consumption, diabetes/glucose intolerance, all at baseline in 1987/88, and any major cardiovascular disease from baseline up to 6 months prior to cognitive testing in 2002/03.
relationship with PV in our multivariate analyses. Possibly, differences in treatment of confounding factors explain this discrepancy. Also, PV may only affect cognition at the time of testing. The Caerphilly study also reported a U-shaped relationship between HCT and general cognitive function; a linear relationship with reaction time was reported [13]. We found significant, linear effects of HCT on cognitive decline, particularly when estimated from a pre-morbid level. Also, fibrinogen predicted decline in non-verbal reasoning. Fibrinogen was a risk factor for cognitive decline in both mildly cognitively impaired people [32] and older vascular patients [33]. Although no relationship with fibrinogen was found in the Caerphilly study, slower reaction times were seen in those in the highest quartile of fibrinogen levels [13].

Previously, BV, PV and HCT increased the risk of coronary events [34, 35] and stroke [36]. BV is a predictor of incident stroke [11]. Early atherosclerosis may link blood rheology and vascular events [10]. A low ankle-brachial index also predicted decline in information processing speed [36]. Here, the main associations were independent of major CVD. Possibly, the cognitive impact of blood rheology may be direct, although we cannot rule out mediating effects of subclinical atherosclerosis.

Fibrinogen is an inflammatory marker involved in platelet activation and blood coagulation. Fibrinogen predicts coronary events and stroke [37], although it is unclear whether increased fibrinogen is a cause of thrombotic disease or consequence [38]. There is evidence that fibrinogen may be associated with clinically silent cerebral lesions in stroke-free individuals [39]. Cerebral infarcts are associated with cognitive impairment and dementia [40] and may mediate the cognitive effects of fibrinogen. Also, important changes in rheology occur with age that may affect cognition in older people. Increases in BV, PV and red cell aggregation have been reported [9, 12]. Decreased red cell deformability may impair the passage of red cells through the microcirculation. Such alterations correlate with impaired cerebral blood flow [12]. We found that relative BV, an indicator of red cell deformability, independently predicted cognitive function.

Possible limitations need to be discussed. Firstly, only 452 subjects participated in follow-up cognitive testing (28% of the original sample, 63% of those participating in baseline cognitive testing in 1998/99). Our sample also had a better health profile at baseline; if these subjects also had better blood rheology, then our associations are likely to be underestimated but not invalid. Indeed, sample attrition of similar extent has been noted in other longitudinal studies, including the Honolulu-Asia Aging Study [41]. Also, our rheology data came from a single measurement; any instability in the levels of these markers would result in our findings being conservative estimates of their true level. Stronger associations were seen between the NART and rheology markers than between these and some cognitive tests, underscoring the importance of controlling for pre-morbid cognition. Controlling for the NART offered an estimate of ‘cognitive change’ across an effectively much longer period than the actual 4-year follow-up [30]. Also, we administered cognitive tests on two separate occasions. The observed, absolute amount of cognitive decline might be an underestimation of the true extent of change due to practice effects affecting some tests. This is unlikely to affect individual differences in cognitive change which we modelled here. Administering several tests for each cognitive domain, particularly executive function, needs consideration in future studies as opposed to our use of only a single test of each major domain. Executive function was assessed using only a brief, simple measure of word fluency. It is possible that on its own this test did not adequately reflect the complexity and importance of this cognitive domain.

In conclusion, the rheological properties of blood are important determinants of circulatory flow behaviour. This study shows that these are also independently associated with cognition function. The impact of blood rheology on cognition may be at a par with more established CVD risk factors. Future studies need to determine whether these markers can be considered as targets for strategies aiming at preventing or delaying cognitive decline in older people.

Key points

- Cardiovascular risk factors and diseases can negatively impact cognitive function in older people.
- Determinants of the flow of blood in the circulation are implicated in atherogenesis, thrombogenesis and acute vascular events.
- Few studies have investigated the relationship between cognition and blood rheology or the flow resistance of blood.
- The present study found that different markers of blood rheology were associated with an increased cognitive decline.
- Whether blood rheology makes a useful target for preventing or delaying cognitive decline needs to be investigated.

Conflicts of interest

None.

Supplementary data

Supplementary data are available at Age and Ageing online.

References


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