Neuropsychological profiles of vascular disease and risk of dementia

Citation for published version:

Digital Object Identifier (DOI):
10.1093/ageing/afx016

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Age and Ageing

Publisher Rights Statement:
The Author 2017. Published by Oxford University Press on behalf of the British Geriatrics Society. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
Neuropsychological profiles of vascular disease and risk of dementia: implications for defining vascular cognitive impairment no dementia (VCI-ND)

BLOSSOM CHRISTA MAREE STEPHAN1, THAIS MINETT2, GRACIELA MUNIZ-TERRERA3, STEPHANIE L HARRISON1, FIONA E MATTHEWS4, CAROL BRAYNE2

1Newcastle University – Newcastle University Institute for Ageing and Institute of Health and Society, Newcastle upon Tyne, Tyne and Wear, UK
2University of Cambridge – Institute of Public Health, Cambridge, UK
3University of Edinburgh – Centre for Dementia Prevention, Edinburgh, Scotland
4MRC Biostatistics Unit – University of Cambridge, Cambridge CB2 2SR, UK

Address correspondence to: B. C. M. Stephan. Tel: +44 (0)191 208 3811; Fax: +44 (0)191 208 1101.
Email: blossom.stephan@ncl.ac.uk

Abstract

Background: vascular cognitive impairment no dementia (VCI-ND) defines a preclinical phase of cognitive decline associated with vascular disorders. The neuropsychological profile of VCI-ND may vary according to different vascular conditions.

Objective: to determine the neuropsychological profile of individuals with no dementia and vascular disorders, including hypertension, peripheral vascular disease (PVD), coronary heart disease (CHD), diabetes and stroke. Risk of 2-year incident dementia in individuals with disease and cognitive impairment was also tested.

Methods: participants were from the Cognitive Function and Ageing Study. At baseline, 13,004 individuals aged ≥65 years were enrolled into the study. Individuals were grouped by baseline disorder status (present, absent) for each condition. Cognitive performance was assessed using the Mini Mental State Examination (MMSE) and the Cambridge Cognitive Examination (CAMCOG). Dementia was assessed at 2 years.

Results: in the cross-sectional analysis, hypertension, PVD and CHD were not associated with cognitive impairment. Stroke was associated with impaired global (MMSE) and CAMCOG sub-scale (including memory and non-memory) scores. Diabetes was associated with impairments in global cognitive function (MMSE) and abstract thinking. In the longitudinal analysis, cognitive impairments were associated with incident dementia in all groups.

Conclusion: the neuropsychological profile in individuals with vascular disorders depends on the specific condition investigated. In all conditions cognitive impairment is a risk factor for dementia. A better understanding of which cognitive domains are affected in different disease groups could help improve operationalisation of the neuropsychological criteria for VCI-ND and could also aid with the development of dementia risk prediction models in persons with vascular disease.

Keywords: vascular cognitive impairment no dementia, vascular disease, cognition, dementia risk, epidemiology, older people

Introduction

Cognitive impairment secondary to the onset of vascular disorders has been termed vascular cognitive impairment (VCI) [1–3]. Clinically VCI can manifest as vascular dementia (either pure or mixed with Alzheimer’s pathology) or as vascular cognitive impairment no dementia (VCI-ND), a prodromal condition associated with increased dementia risk [4]. The underlying causes of vascular disorders have different pathological mechanisms (such as embolic and thrombotic infarcts, haemorrhagic strokes, small vessel disease) and the presence of co-morbidities such as AD pathology. Such heterogeneity makes VCI difficult to diagnose added to the fact that no standardised operational criteria exist.
Cerebrovascular diseases have been shown to be usually associated with cognitive impairment related to fronto-cortical connections, including executive function and speed, rather than being memory related as typically seen in AD [5]. However, this pattern is not always observed, and cognitive changes associated with VCI can be variable. For example, in individuals with stroke impairment in global functioning, memory and non-memory domains have all been observed [6, 7]. In stroke patients the pattern of cognitive impairment may depend on the location and severity of infarction. With regard to hypertension, one study found impaired long-term memory and executive functioning in hypertensive cases [8], in another study hypertension was found to be associated with memory performance in men only [9], in a third study [10] no cognitive differences were found when non-hypertensive and medicated hypertensive groups were compared and lastly, in a fourth study longitudinal evidence suggested an association between hypertension and cognitive decline at mid-life, but not in late-life [11]. In individuals with diabetes cognitive impairment has been observed in global function, memory and non-memory (including executive and speed) domains [12, 13]. Peripheral vascular disease (PVD) and coronary heart disease (CHD) have also been associated with cognitive impairments across a variety of domains [14].

As highlighted in the paragraph above, no consistent pattern of cognitive impairment has been observed across different vascular conditions. Cognitive performance has not been compared within the same cohort for different vascular conditions using a population representative framework. This study therefore addresses this gap. A better understanding of the clinical features associated with different health conditions is important for the development of patient assessment protocols (i.e. in particular, for informing diagnostic criteria for VCI) and considerations for intervention; for example, not only health but also cognition. The aim of this study is to assess risk of cognitive impairment in both global and domain-specific tasks and risk of 2-year incident dementia in individuals with vascular-related co-morbidities, including hypertension, PVD, CHD, diabetes and stroke.

**Methods**

**Participants**

Data were from the Cognitive Function and Ageing Study (CFAS) [15]. Individuals aged ≥65 years were randomly selected from the Family Health Service Authority lists in Cambridgeshire, Gwynedd, Newcastle, Nottingham and Oxford. Baseline interviewing began in 1991. A two-phased screening procedure was used. At baseline screening, 13,004 participants provided information on socio-demographic status, health, functional ability and cognitive performance measured using the Mini Mental State Examination (MMSE) [16]. Selected items from the Geriatric Mental State (GMS) Automated Geriatric Examination for Computer-Assisted Taxonomy (AGECAT) [17] were also administered. All interviews were undertaken at the participants’ place of residence by a trained interviewer.

Following the baseline interview, a sub-sample of approximately 20% (n = 2,640) were selected based on cognitive ability, age and centre (weighted towards older and more cognitively frail individuals) to complete a more detailed assessment (the B3 version of the full GMS which has AGECAT algorithms used for automated study diagnosis), the Cambridge Cognitive Examination (CAMCOG) (augmented) and repeat cognitive testing using the MMSE. Participants were re-interviewed approximately every 2 years. Local Research Ethics Committee approval was attained at each study site. All participants gave informed consent before interview.

**Dementia status**

Dementia diagnosis is based on the full AGECAT diagnostic algorithm, defined as an organicity rating case level of 3 or above [17] which is similar to a diagnosis based on the Diagnostic and Statistical Manual (DSM) 3rd Revision [18]. Dementia was diagnosed independently of the MMSE and CAMCOG results.

**Health status**

From the baseline interview five conditions that have been associated with an increase in prevalence in older aged populations were selected, including hypertension, PVD, CHD, diabetes and a history of stroke. Hypertension, stroke and diabetes were assessed using participant self-report. Participants reporting currently receiving medication for hypertension were coded as having the disorder. For diabetes, participants who reported the condition or taking anti-diabetic medication were coded as having diabetes. Stroke was assessed using a single question asking about the presence or absence of the condition. Angina and PVD were derived from Diagnostic Scales [19]. CHD was a composite variable incorporating the presence of self-reported heart attack (single question asking about the presence or absence of the condition) or angina based on the Rose Diagnostic Scale.

**Neuropsychological evaluation**

Global cognitive function was assessed using the MMSE (range 0–30) and the total score on the CAMCOG (range 0–103). Domain-specific performance was measured using the CAMCOG sub-scales, including orientation, language (comprehension, expression), perception, memory (learning, recent, remote), praxis, abstract thinking and attention and calculation. Scores for the MMSE and CAMCOG were dichotomised into impaired versus not-impaired. For the CAMCOG total and sub-scales scores, impairment was defined as a score below the 25th percentile on each scale using normative values derived in non-demented individuals [20]. For the MMSE, scores less than 24 were taken to reflect impairment [21].
Analysis

Prevalence of the disorder and no-disorder groups for people without dementia across the five conditions was calculated, weighted for study design. Across the five conditions, differences in demographics between the disorder and no-disorder groups were compared using t-tests (continuous variables) or the chi-squared test (categorical variables). Logistic regression (weighted for study design) controlling for education, age, and disease co-morbidity was used to estimate the odds ratios (ORs) for cognitive impairment (MMSE and CAMCOG scores) across each of the five health conditions. The disease co-morbidity score was calculated as the sum of the conditions minus the disease of interest [22].

Associations between the cognitive test scores and 2-year risk of dementia in each disorder group were tested using Poisson regression controlling age, sex, years of education and disease co-morbidity. For persons with dementia time was defined as the mid-point between the first assessment and the 2-year follow-up interview. To adjust for oversampling of individuals aged 75 and older and sampling to the national population, all results were backweighted according to age, sampling group at screening and interview version using inverse probability weights. Loss to follow-up was also adjusted for in the analysis. All analyses were completed using STATA Version 14.

Results

Demographics of the 2,640 individuals seen at the first assessment 587 were diagnosed with dementia and were excluded. Prevalence varied across the different conditions: 27.5% (95% CI: 24.9–30.1) reported hypertension, 21.4% (95% CI: 19.1–23.9) CHD, 7.3% (95% CI: 6.0–8.8) stroke, 5.2% (95% CI: 4.1–6.6) diabetes and 4.4% (95% CI: 3.4–5.9) PVD. Table 1 shows the demographic profiles of the disorder and no-disorder groups for each condition in individuals without dementia. Individuals with hypertension (P = 0.004) and stroke (P = 0.032) were more likely to be women, and for PVD there were more men (P = 0.002). Only hypertension showed a significant age difference; people with hypertension were younger than those with no history of hypertension (P = 0.002). No significant difference in educational level was found between the disorder present and absent groups for any conditions.

Of the 2,050 individuals without dementia at the first assessment 49.8% (n = 1,021) had none of the five conditions, 29.7% (n = 608) had one condition, 13.4% (n = 274) had two conditions, 2.9% (n = 61) had three conditions, 0.5% (n = 10) had four conditions and 3.7% (n = 76) were missing disease status information for one or more of the conditions. Table 2 shows the pattern of disease co-morbidity across the different conditions.

Cognitive Function Cross-sectional Results Supplementary data, Table 1, available in Age and Ageing online displays the ORs and 95% confidence intervals (CIs) for each of the cognitive variables predicted by each health condition when adjusting for age, sex, education and disease co-morbidity. The pattern of cognitive impairments varied across the different conditions. Hypertension, PVD and CHD were not associated with impairment on any measure. In contrast, compared to participants without diabetes, those with diabetes were more likely to be impaired on the MMSE (OR = 1.66; 95% CI: 1.00–2.76) and CAMCOG sub-scale score of abstract thinking (OR = 1.78; 95% CI: 1.01–3.15). Participants with stroke performed significantly worse than those without stroke on the CAMCOG sub-scale scores of orientation (OR = 2.25; 95% CI: 1.40–3.61), language comprehension (OR = 1.80; 95% CI: 1.10–2.95), learning memory (OR = 1.67; 95% CI: 1.05–2.65), praxis (OR = 1.64; 95% CI: 1.03–2.62) and perception (OR = 1.74; 95% CI: 1.02–2.98).

Two-year Incident Dementia: Of the 2,050 individuals without dementia seen at the first assessment, at 2-year follow-up 230 had died, 440 refused or were lost to follow-up and 26 had moved. Dementia status at 2 years was known in 1,347 individuals: 1,210 non-demented and 137 with incident dementia. Table 3 shows the results of the association between cognitive function and risk of dementia, when controlling for age, sex, education and disease co-morbidity for

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>PVD</th>
<th>CHD</th>
<th>Diabetes</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>n</td>
<td>1,450</td>
<td>576</td>
<td>1,904</td>
<td>87</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>76.1 (7.4)</td>
<td>74.8 (6.5)</td>
<td>75.6 (7.3)</td>
<td>75.9 (6.8)</td>
</tr>
<tr>
<td>% Women (%)</td>
<td>61.0 (885)</td>
<td>67.9 (391)</td>
<td>63.6 (1210)</td>
<td>47.1 (41)</td>
</tr>
<tr>
<td>Mean years full-time education (SD)</td>
<td>9.7 (2.1)</td>
<td>9.6 (2.0)</td>
<td>9.7 (2.1)</td>
<td>9.4 (1.3)</td>
</tr>
</tbody>
</table>

Note: Bold indicates significant differences between those with and without the condition.

Table 2. Pattern of disease co-morbidity (number) across the different conditions

Table 1. Sample demographics stratified by the presence/absence of the condition (non-demented individuals)

*Note that the total number of participants in the CFAS assessment arm with no dementia was 2,050.
Table 3. Associations (Poisson Regression Analysis) between cognitive function and risk of 2-year incident dementia in each condition separately (controlling baseline age, sex, years of education and disease co-morbidity) weighted for study design and loss to follow-up

<table>
<thead>
<tr>
<th></th>
<th>Hypertension group</th>
<th>PVD group</th>
<th>CHD group</th>
<th>Diabetes group</th>
<th>Stroke group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta coefficient</td>
<td>95% CI</td>
<td>Beta coefficient</td>
<td>95% CI</td>
<td>Beta coefficient</td>
</tr>
<tr>
<td>MMSE</td>
<td>1.79</td>
<td>(0.76–2.81)</td>
<td>1.04</td>
<td>(–1.00–3.07)</td>
<td>2.73</td>
</tr>
<tr>
<td>CAMCOG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Score</td>
<td>1.02</td>
<td>(–0.07–2.11)</td>
<td>1.69</td>
<td>(–2.34–5.72)</td>
<td>1.88</td>
</tr>
<tr>
<td>Orientation</td>
<td>1.46</td>
<td>(0.33–2.59)</td>
<td>2.04</td>
<td>(–1.78–5.85)</td>
<td>2.73</td>
</tr>
<tr>
<td>Language comprehension</td>
<td>0.26</td>
<td>(–0.67–1.19)</td>
<td>2.89</td>
<td>(–0.26–6.04)</td>
<td>0.74</td>
</tr>
<tr>
<td>Language expression</td>
<td>0.93</td>
<td>(–0.23–2.10)</td>
<td>19.06</td>
<td>(16.8–21.32)</td>
<td>1.07</td>
</tr>
<tr>
<td>Remote memory</td>
<td>0.53</td>
<td>(–0.47–1.52)</td>
<td>–2.47</td>
<td>(–6.35–1.40)</td>
<td>0.93</td>
</tr>
<tr>
<td>Recent memory</td>
<td>0.82</td>
<td>(–0.06–1.70)</td>
<td>–1.99</td>
<td>(–5.00–1.02)</td>
<td>1.65</td>
</tr>
<tr>
<td>Learning memory</td>
<td>0.95</td>
<td>(0.08–1.82)</td>
<td>–0.75</td>
<td>(–4.80–3.30)</td>
<td>1.37</td>
</tr>
<tr>
<td>Attention and calculation</td>
<td>0.35</td>
<td>(–0.56–1.26)</td>
<td>2.60</td>
<td>(–0.33–5.54)</td>
<td>1.43</td>
</tr>
<tr>
<td>Praxis</td>
<td>0.41</td>
<td>(–0.57–1.38)</td>
<td>–0.35</td>
<td>(–4.50–3.80)</td>
<td>1.12</td>
</tr>
<tr>
<td>Abstract thinking</td>
<td>0.27</td>
<td>(–0.68–1.22)</td>
<td>21.05</td>
<td>(18.43–23.66)</td>
<td>0.75</td>
</tr>
<tr>
<td>Perception</td>
<td>0.32</td>
<td>(–0.67–1.30)</td>
<td>2.03</td>
<td>(–0.96–5.03)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Note: Bold indicates significant differences (P < 0.05), i.e. where the Beta coefficient is significantly different from zero.

Discussion

In this population-based study we found that different vascular-related disorders were associated with different patterns of cognitive impairment. In individuals with hypertension and diabetes, impairments in the MMSE, CAMCOG total score and CAMCOG sub-scales of language expression, memory (recent and learning), praxis and perception were associated with increased risk of dementia in individuals with diabetes. In individuals with diabetes, impairments in the MMSE, CAMCOG total score and CAMCOG sub-scales of language expression and abstract thinking were associated with increased risk of dementia. In individuals with diabetes, impairments in the MMSE, CAMCOG total score and CAMCOG sub-scales of language expression and abstract thinking were associated with increased risk of dementia. In individuals with diabetes, impairments in the MMSE, CAMCOG total score and CAMCOG sub-scales of language expression and abstract thinking were associated with increased risk of dementia.
cognitive-disorder associations observed here do not appear to be due to a reduction in reserve, associated for example with educational attainment, as this did not differ significantly in the disorder and no-disorder groups for each condition and was controlled in the analyses. It could be that cognitive decline may be associated with impaired vascular function and future studies are needed to test the association between cognitive decline and incident disease. Alternatively, results suggest that changes may be linked to the specific vascular disorder. It could be that the effects of each vascular condition on cognition are related to their underlying pathogenesis as well as on the anatomical location of the vascular damage. For example, hypertension is a risk factor for the more severe conditions included in this analysis [23]. Hypertension increases atherosclerotic risk and is a major risk factor for heart attack and ischaemic stroke through the disruption of normal blood flow [24]. In addition, high blood pressure is a primary risk factor for haemorrhagic stroke due to the increased vascular susceptibility to rupture in the brain [25]. CHD is characterised by a greater vascular pathology but the organ specificity of vascular dysfunction in CHD may have a sparing effect on the brain vascular system and may explain the lower impact on cognitive function compared to stroke patients [26, 27]. Insulin resistance and chronic hyperglycaemia are major features of type 2 diabetes, which may alter the normal regulation of blood flow and modify neuronal cellular metabolism [28]. All the previous conditions increase the risk of stroke, which may therefore represent the final outcome of the cumulative effects of vascular and metabolic dysfunction on the brain and explain the greater impact of stroke on cognition.

Results from the longitudinal analysis found that different cognitive impairments were associated with risk of 2-year incident dementia across the different conditions. Of note is that while in the cross-sectional analysis the disease and no-disease groups did not differ significantly on any cognitive measure for hypertension, PVD and CHD, in the longitudinal analysis we found that impaired cognition in the presence of disease was associated with an increased risk of 2-year incident dementia compared to persons with disease but no cognitive impairment. Importantly, cognitive measures may be incorporated into prediction models to better determine who has the highest risk of dementia amongst persons with co-morbid vascular disease. Further, these may be targets to prevent further cognitive decline and progression to dementia in persons with co-morbid vascular disease.

This study is limited by the use of self-reported disease status. However, self-reported and objective disorder status have previously been found to be in high agreement for the disorders included [29, 30]. Other conditions of interest including, for example, dyslipidemia and obesity are not available in CFAS and given the increase in prevalence of these with ageing it would be important to also determine the pattern of cognitive impairments associated with each. Information on disease severity is not available and this could impact disease-cognition associations. Cognition was assessed using the MMSE and CAMCOG and other batteries recommended for testing cognition within the context of VCI-ND, such as the Montreal Cognitive Assessment (MoCA), are not available in CFAS. Nevertheless, using the MMSE and CAMCOG both global and domain-specific function across multiple subdomains could be assessed.

Conclusion

Identification of VCI-ND is a challenge due to variation in cognitive profiles across the different disorders and lack of operational criteria. The findings suggest that the neuropsychological tests used for cognitive screening in vascular disorders should be selected based on knowledge of the underlying vascular condition, or where this is not known, tests should tap as broad as domains as possible. A better understanding of the cognitive risks associated with different health conditions would improve criteria for VCI-ND and help with the development of risk models for predicting dementia in persons with vascular disease.

Key points

- There is large variation in the cognitive profiles across different vascular disorders.
- Variation in the cognitive profiles of different vascular disorders has implications for the development of neuropsychological criteria for VCI-ND.
- Poor cognitive function is a risk factor for 2-year incident dementia in persons with hypertension, PVD, CHD, diabetes and stroke; with different domains associated with dementia risk depending on the underlying condition.
- A better understanding of the cognitive risks associated with different health conditions would improve criteria for VCI-ND.

Supplementary data

Supplementary data are available at Age and Ageing online.

Acknowledgements

We would like to thank the CFAS participants, their families and carers for taking part in the study.

Conflict of interests

None declared.

Funding

MRC CFAS has been funded by the Medical Research Council (G9901400) and Department of Health.
Ethical approval

CFAS was approved by the local ethics committee and has multicentre ethics committee approval (Ethics Approval Reference 05/mrec05/37).

References


Received 8 April 2016; editorial decision 13 December 2016