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Neuropsychological Profiles of Vascular Disease and Risk of Dementia: Implications for Defining Vascular Cognitive Impairment no Dementia (VCI-ND)

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 two-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 two-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-domain (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.

Conclusions—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 (VCI-ND); Vascular Disease; Cognition; Dementia Risk; Epidemiology

Ethics

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

Competing Interests

No author has any conflict of interest to declare.

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 two-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 re-interviewed approximately every two 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].

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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 age, sex, years of education 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 two-year risk of dementia in each disorder group were tested using Poisson regression controlling for 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 two-year follow-up interview. To adjust for oversampling of individuals aged 75 and older and sampling to the diagnostic interview, 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% 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 Table 2 displays the odds ratios and 95% confidence intervals 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

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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-domain 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-years Incident Dementia

Of the 2,050 individuals without dementia seen at the first assessment, at two-years follow-up 230 had died, 440 refused a follow-up interview, and 26 had moved. Dementia status at two-years was known in 1,641 individuals: 1,210 non-demented and 137 with 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 each condition. As shown, in individuals with hypertension impairments in the MMSE and CAMCOG subdomains of orientation and learning memory were associated with risk of dementia. In individuals with PVD impairments in the CAMCOG subdomains of language expression and abstract thinking were associated with risk of dementia. In individuals with CHD impairments in the MMSE, CAMCOG total and subdomains scores of memory (recent and learning), attention and calculation and praxis were associated with risk of dementia. In individuals with diabetes impairments in the MMSE, CAMCOG total score and CAMCOG subdomains of orientation, language expression, memory (remote and learning), praxis and perception were associated with risk of dementia. In individuals with stroke, cognitive impairment in the MMSE, CAMCOG total score and CAMCOG subdomains of language expression, memory (remote, recent and learning), attention and calculation and praxis were associated with risk of dementia.

Discussion

In this population based study we found that different vascular disorders were associated with different patterns of cognitive impairment and that the extent of cognitive impairment increased with the severity of vascular dysfunction. There was little evidence that hypertension, CHD or PVD were associated with an increased risk of cognitive impairment. In contrast, diabetes was significantly associated with impaired global cognitive function (MMSE score) and the CAMCOG sub-scale score of abstract thinking. Cognitive impairment was most apparent in individuals with stroke. In contrast, in longitudinal analyses, risk of dementia was associated with cognitive impairments at baseline in all groups; although different patterns of impairment were associated with dementia risk across the different conditions. The results have implications for how VCI-ND should be operationalised, particularly in terms of the choice of domains of cognitive functioning that should be assessed across different conditions.

Considerable debate exists regarding the nature of the cognitive deficits associated with VCI-ND. Even in the absence of dementia and when controlling for covariates, in cross-sectional analyses, we found that diabetes is associated with global deficits and impaired abstract thinking and that stroke is associated with impairment across multiple domains including: global, memory and non-memory. Hypertension, PVD and CHD were not found to be associated with impairments in the MMSE or CAMCOG total or sub-domain scores. These results support findings from some, but not all studies. Differences across studies could be explained by methodological differences including for example, choice of cognitive tests, definition of disease and sample specific characteristics (e.g. population-based vs. clinical). Further exploration of the pattern of preservation and impairment across different cognitive domains and vascular conditions is needed.

The underlying mechanism by which vascular disease affects cognitive performance is poorly understood. The 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 ischemic 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 two-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 presence of disease was associated with an increased risk of two 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 cardio-metabolic diseases. 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-report disease status. However, self-reported and objective disorder status has previously been found to be in high agreement for the disorders

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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 VCIND, 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 sub-domains 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 Vascular Cognitive Impairment no Dementia (VCI-ND).
- Poor cognitive function is a risk factor for two-year incident dementia in persons with hypertension, peripheral vascular disease, coronary heart disease, 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.

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Table 1

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

	Hypertension		PVD		CHD		Diabetes		Stroke	
	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present
n*	1,450	576	1,904	87	1,567	450	1,904	129	1,836	197
Mean Age (SD)	**76.1 (7.4)**	**74.8 (6.5)**	75.6 (7.3)	75.9 (6.8)	75.6 (7.3)	75.8 (7.1)	75.7 (7.3)	75.6 (6.2)	75.7 (7.3)	76.2 (6.9)
% Women (n)	**61.0 (885)**	**67.9 (391)**	**63.6 (1210)**	**47.1 (41)**	64.0 (1003)	59.1 (266)	63.1 (1201)	60.5 (78)	**63.6 (1168)**	**55.8 (110)**
Mean Years Full Time Education (SD)	9.7 (2.1)	9.6 (2.0)	9.7 (2.1)	9.4 (1.3)	9.7 (2.1)	9.6 (1.9)	9.7 (2.1)	9.7 (1.7)	9.7 (2.1)	9.5 (2.0)

Key

*Note that the total number of participants in the CFAS assessment arm with no dementia was 2,053

Note

Bold indicates significant differences between those with and without the condition

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Table 2

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

	Hypertension	PVD	CHD	Diabetes	Stroke
Hypertension (n=576)		29	168	56	98
PVD (n=87)			40	11	16
CHD (n=450)				40	69
Diabetes (n=129)					19
Stroke (n=197)					

Table 3

Associations (Poisson Regression Analysis) between cognitive function and risk of two-year incident dementia in each condition separately (controlling for baseline age, sex, years of education and disease co-morbidity) weighted for study design and loss to follow-up

	Hypertension Group		PVD Group		CHD Group		Diabetes Group		Stroke Group	
	Beta Coefficient	**95%CI**	**Beta Coefficient**	**95%CI**	**Beta Coefficient**	**95%CI**	**Beta Coefficient**	**95%CI**	**Beta Coefficient**	**95%CI**
MMSE	**1.79**	**(0.76-2.81)**	1.04	(-1.00-3.07)	**2.73**	**(1.68-3.77)**	**17.85**	**(16.68-19.02)**	2.00	(0.77-3.24)
CAMCOG										
- Total Score	1.02	(-0.07-2.11)	1.69	(-2.34-5.72)	**1.88**	**(0.63-3.14)**	**17.77**	**(15.33-20.21)**	**4.20**	**(1.99-6.42)**
- Orientation	**1.46**	**(0.33-2.59)**	2.04	(-1.78-5.85)	0.46	(-0.44-1.36)	**2.91**	**(0.45-5.37)**	0.07	(-1.29-1.44)
- Language comprehension	0.26	(-0.67-1.19)	2.89	(-0.26-6.04)	0.74	(-0.25-1.74)	-0.24	(-2.90-2.42)	0.54	(-0.94-2.01)
- Language expression	0.93	(-0.23-2.10)	**19.06**	**(16.8-21.32)**	1.07	(-0.29-2.43)	**15.98**	**(13.97-18.00)**	**1.93**	**(0.09-3.77)**
- Remote memory	0.53	(-0.47-1.52)	-2.47	(-6.35-1.40)	0.93	(-0.12-1.98)	**16.87**	**(14.94-18.80)**	**1.44**	**(0.29-2.58)**
- Recent memory	0.82	(-0.06-1.70)	-1.99	(-5.00-1.02)	**1.65**	**(0.67-2.62)**	0.39	(-2.45-3.24)	**2.03**	**(0.59-3.47)**
- Learning memory	**0.95**	**(0.08-1.82)**	-0.75	(-4.80-3.30)	**1.37**	**(0.36-2.38)**	**18.21**	**(16.2-20.21)**	**2.48**	**(0.68-4.28)**
- Attention and calculation	0.35	(-0.56-1.26)	2.60	(-0.33-5.54)	**1.43**	**(0.14-2.71)**	1.24	(-0.83-3.30)	**1.55**	**(0.11-2.98)**
- Praxis	0.41	(-0.57-1.38)	-0.35	(-4.50-3.80)	**1.12**	**(0.09-2.16)**	**17.78**	**(15.66-19.90)**	**2.21**	**(0.61-3.82)**
- Abstract thinking	0.27	(-0.68-1.22)	**21.05**	**(18.43-23.66)**	0.75	(-0.23-1.74)	-1.12	(-3.70-1.46)	1.10	(-0.41-2.61)
- Perception	0.32	(-0.67-1.30)	2.03	(-0.96-5.03)	0.81	(-0.29-1.92)	**16.80**	**(14.47-19.12)**	1.06	(-0.26-2.38)

Notes Bold indicates significant differences ($p<0.05$) i.e. where the Beta coefficient is significantly different from zero