Dementia prediction for people with stroke in populations: is mild cognitive impairment a useful concept?

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Abstract

Background: criteria for mild cognitive impairment (MCI) capture an intermediate cognitive state between normal ageing and dementia, associated with increased dementia risk. Whether criteria for MCI are applicable in the context of stroke and can be used to predict dementia in stroke cases is not known.

Objectives: to determine the prevalence of MCI in individuals with stroke and identify predictors of 2-year incident dementia in stroke cases.

Methods: individuals were from the Medical Research Council Cognitive Function and Ageing Study. MCI prevalence in individuals with stroke was determined. Logistic regression, with receiver operating characteristic curve analysis, was used to identify variables associated with risk of dementia in stroke cases including MCI criteria, demographic, health and lifestyle variables.

Findings: of 2,640 individuals seen at the first assessment, 199 reported stroke with no dementia. In individuals with stroke, criteria for MCI are not appropriate, with less than 1% of stroke cases being classified as having MCI. However, in individuals with stroke two components of the MCI definition, subjective memory complaint and cognitive function (memory and praxis scores) predicted 2-year incident dementia (area under the curve = 0.85, 95% CI: 0.77–0.94, n = 113).

Conclusion: criteria for MCI do not appear to capture risk of dementia in the context of stroke in the population. In stroke cases, subjective and objective cognitive performance predicts dementia and these variables could possibly be incorporated into dementia risk models for stroke cases. Identifying individuals with stroke at greatest risk of dementia has important implications for treatment and intervention.

Keywords: stroke, dementia, mild cognitive impairment, risk, epidemiology, older people

Introduction

Stroke is associated with an increased risk of cognitive impairment and dementia [1, 2]. How best to capture those individuals with mild impairment in cognition and at increased risk of dementia secondary to stroke in population-based cohorts is not currently known. The term vascular cognitive impairment no dementia (VCIND) refers to the mildest form of cognitive impairment related to cerebrovascular diseases and is associated with elevated risk of dementia [3, 4]. However, there are currently no standard criteria for diagnosing VCIND across the many different vascular conditions such as stroke and hypertension. Further, there is wide variation in how different studies classify such individuals and this usually depends on the data available (e.g. given health condition, neuropsychological test, whether brain MRI was undertaken). Lack of consensus impedes cross-study comparability and undermines the
validity of this concept. Stratification of stroke cases into more homogeneous groups, for example in terms of cognitive functioning (e.g. impaired versus not-impaired) and risk of dementia (at-risk versus not-at risk), will be important for clinical trial enrolment within the context of VCIND as well as for improving routine care.

Within the framework of Alzheimer’s disease, preclinical cognitive impairment is usually captured using the term mild cognitive impairment (MCI) as defined by Petersen et al. [5] and includes the following: subjective memory complaint (SMC), normal general cognitive function, objective cognitive deficit, maintenance of function and no dementia. Typically, the most prominent feature of MCI is an impairment in memory performance (e.g. amnestic MCI: aMCI), but non-memory (e.g. non-amnestic MCI: nMCI) and multi-domain sub-types (e.g. multi-domain MCI: mMCI) also exist [6]. The applicability of MCI criteria for capturing cognitive impairment and risk of dementia associated with stroke is not known and is explored here. We also test the predictive accuracy of conventional risk factors to predict 2-year incident dementia in stroke cases including demographic, cognitive, health, lifestyle and physical functioning variables.

Methods

Participants

This study was embedded within the Medical Research Council Cognitive Function and Ageing Study (CFAS), a population representative cohort of individuals aged 65 years and older recruited from registers of primary care physicians in five UK centres using identical methodology. Full details of the study design have been published previously [7]. In brief, baseline interviewing began in 1991 and in total, 13,004 individuals were recruited (82% response rate). A 20% (n = 2,640) stratified sample, selected based on cognitive ability, age and centre completed a more detailed assessment interview, with re-interviewing at 2 years. Information on demographics (age, gender and years of education), self-reported health (including chronic conditions), cognition and functional ability were collected by computerised interviews conducted at the participant’s place of residence by a trained interviewer. Data from the initial prevalence screen, first assessment and 2-year follow-up interviews (Data Version 9.0) were used in this analysis.

Ethics

All participants gave informed consent before the interview. When participants could not consent for themselves, for example due to severe cognitive impairment, consent was obtained by their informant.

Dementia diagnosis

Dementia was diagnosed using the Geriatric Mental State Examination Automated Geriatric Examination for Computer-Assisted Taxonomy (AGECAT) diagnostic algorithms [8] and defined as an AGECAT organic symptom level of 3 or greater. This has been found to be comparable to dementia as diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, Revised (DSM-III-R) [9].

Neuropsychological evaluation

Global cognition was assessed at each interview using the Mini-Mental State Examination (MMSE) [10]. A MMSE score of 21 or less was taken to reflect impairment when defining MCI. Domain-specific cognitive function was assessed using the Cambridge Cognitive Examination (CAMCOG) [11] (augmented in that items on tactile recognition of coins were excluded). For the CAMCOG, a total score assessing overall ability was calculated (range: 0–103). Sub-scale scores were also derived for memory including learning, recent and remote memory and non-memory domains including orientation, language comprehension and expression, perception, praxis, abstraction and attention and calculation. Summing scores only from the memory or non-memory sub-scales created composite scores. As the CAMCOG scores (total, sub-scale and composite memory and non-memory scores) were not normally distributed, impairment for each domain and the composite memory and non-memory scores was defined using a cut-off score of 1 SD below the mean (16th centile), adjusted for age.

Physical function

Performance on activities of daily living (ADL) and instrumental activities of daily living (IADL) was assessed using items from the Modified Townsend Disability Scale [12]. Using information on the hierarchy of ADL and IADL disability, individuals were classified as (i) severely impaired (if the person is housebound or requires help at least several times per week with washing, cooking and dressing), (ii) mildly impaired (if the person requires help regularly with heavy housework or shopping and carrying heavy bags) and (iii) not-impaired (if no help is needed with washing, hot meals, shoes and socks, heavy housework or shopping and carrying heavy bags and the individual can get around outside).

Stroke cases

Stroke was assessed at the baseline interview and again at the first assessment interview using a single question—baseline interview: ‘Have you ever had a stroke that required medical attention’, and assessment interview: where there is observation of paralysis ‘What did your doctor say was wrong with your ....? Was the possibility of a stroke mentioned?’. Of the 2,640 individuals seen at the first assessment, 283 reported stroke (at either the baseline or assessment interview), 2,232 were stroke free and 125 individuals had missing stroke status. When excluding individuals with dementia (n = 587), 199 individuals reported stroke and 1,843 were stroke free.
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Diagnosing MCI

As the cognitive deficit in stroke cases is yet to be fully elucidated, in this study we chose to map three different definitions of MCI capturing both domain-specific and multi-domain impairment including (i) Mayo Clinic criteria for aMCI [5], (ii) criteria for nMCI (nMCI: where there is no evidence of memory impairment) and (iii) criteria for mMCI (mMCI: where both memory and non-memory are impaired) [6]. While memory deficits are typically associated with neurodegenerative rather than vascular pathologies, we chose to include aMCI as this is one of the commonly applied definitions of MCI in clinical and research practice. Full details of the operationalisation of each sub-type of MCI in CFAS have been reported in detail previously [13]. For this analysis, no medical exclusions were applied when mapping MCI. At the first assessment, individuals without dementia were classified into three groups including (i) no cognitive impairment (NCI), (ii) MCI or (iii) other cognitive impairment no dementia (OCIND). For classification of MCI, individuals had to fulfil the following criteria: (i) no dementia, (ii) subjective or informant complaint of memory loss, (iii) normal general cognitive function (MMSE ≥ 22), (iv) no or only mild functional impairment and (v) objective memory or non-memory impairment (defined using percentiles (16th centile) to approximate 1 SD below the mean, adjusted for age, derived from the CAMCOG composite memory or non-memory scores). To be classified as NCI, individuals had to fulfil the following criteria: (i) no dementia, (ii) normal general cognitive functioning, (iii) no severe functional impairment and (iv) normal memory and non-memory test performance. The OCIND group included all non-normal, non-demented individuals who failed to fulfil one or more diagnostic criteria for MCI (e.g. individuals without a study diagnosis of dementia, but a MMSE score <22). The OCIND group has been described in detail previously [14].

Analyses

All analyses were completed using Stata version 12 (StataCorp., College Station, TX, USA). Differences in demographics between the stroke and no-stroke groups were compared using t-tests for continuous variables and Chi-squared test for categorical variables. The prevalence of MCI (amnestic, non-amnestic and multi-domain) in stroke cases without dementia was calculated using back weighting for study design. Logistic regression was used to predict the risk of 2-year incident dementia in the stroke group. The following variables were tested in univariable models: demographic [sex, age group (young-old <85 years versus oldest-old ≥85 years) and education (≤9 years versus >9 years)], physical function (ADL/IADL disability), psychiatric status (depression, anxiety), disease co-morbidity (coronary heart disease (CHD) defined as the presence of self-reported heart attack or angina based on the Rose Diagnostic Scale [15], peripheral vascular disease (PVD) defined using the Rose Scale [15], self-reported hypertension and diabetes], lifestyle (current smoking and alcohol consumption) and cognitive function [self or informant memory complaint, MMSE score (dichotomised: ≤24 versus ≥25) [16], CAMCOG total and sub-domain scores (age adjusted)]. Backward stepwise logistic regression (P = 0.2; including only significant variables from the univariable analyses) was used for final model selection. Discriminative accuracy of the final model was assessed using the area under the receiver operator characteristic curve (AUC).

Results

Sample demographics

The prevalence of stroke stratified by study centre, age group and gender has been published previously for the total CFAS population [17], and the demographics of the stroke (n = 283) and no-stroke (n = 2,232) groups are shown in Table 1. Individuals with stroke were more likely to have dementia, fewer years of education, lower MMSE scores, greater functional impairment and increased presence of disease co-morbidity related to CHD, diabetes, hypertension and PVD. Age did not differ between the stroke and no-stroke groups.

MCI criteria in the context of stroke

MCI is rare in individuals with stroke. Less than 1% of individuals with stroke fulfilled criteria for aMCI, nMCI or mMCI. Rather, more individuals with stroke have impairment outside the MCI range, falling into the OCIND category (prevalence of OCIND in stroke cases = 3.4%, 95% CI: 2.7–4.4%). As shown in Table 2, when breaking down the components of the MCI definition over half of the individuals with stroke would be excluded from a MCI diagnosis due to failure to meet the requirement of high physical functioning (46.7% have none/minor ADL/IADL impairment). With respect to the definition of aMCI, very few stroke cases had a pure

Table 1. Characteristics of stroke and no-stroke cases at the first assessment interview

<table>
<thead>
<tr>
<th>Field</th>
<th>No stroke (n = 2,232)</th>
<th>Stroke (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of dementia (a) (%)</td>
<td>17.4 (388)</td>
<td>29.7 (84)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age years (SD)</td>
<td>76.9 (7.7)</td>
<td>77.3 (7.1)</td>
</tr>
<tr>
<td>Mean education years (SD) (a)</td>
<td>9.6 (2.1)</td>
<td>9.3 (1.9)</td>
</tr>
<tr>
<td>Percentage of women (a) (%)</td>
<td>64.5 (1,439)</td>
<td>58.3 (165)</td>
</tr>
<tr>
<td>Mean MMSE (SD) (a)</td>
<td>22.8 (5.4)</td>
<td>20.9 (5.6)</td>
</tr>
<tr>
<td>Health status, % (a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe functional difficulty (a)</td>
<td>25.6 (569)</td>
<td>63.2 (175)</td>
</tr>
<tr>
<td>CHD (a)</td>
<td>19.9 (422)</td>
<td>31.1 (82)</td>
</tr>
<tr>
<td>Diabetes (a)</td>
<td>6.1 (131)</td>
<td>9.5 (26)</td>
</tr>
<tr>
<td>Hypertension (medicated) (a)</td>
<td>24.3 (519)</td>
<td>43.6 (116)</td>
</tr>
<tr>
<td>PVD (a)</td>
<td>3.8 (80)</td>
<td>8.4 (20)</td>
</tr>
</tbody>
</table>

(a) Significance difference between the stroke and no-stroke groups (P < 0.05).

CHD, coronary heart disease; PVD, peripheral vascular disease; SD, standard deviation.
Predicting 2-year incident dementia

Of the 2,640 individuals seen at the first assessment interview, 587 had prevalent dementia and 3 were missing dementia status. These individuals were excluded from further analysis. At 2-year follow-up, there were 137 cases of incident dementia. As shown in Table 3, significant predictors of dementia in individuals with stroke include functional impairment, memory complaint, poor performance on the MMSE and on the CAMCOG (total score and scores on the domains of learning memory, recent memory, attention and calculation, language comprehension and praxis). Results from the backward stepwise regression model found that the most parsimonious model for predicting 2-year incident dementia in the stroke group included SMC and the CAMCOG sub-domain scores of learning memory and praxis (AUC = 0.85, 95% CI: 0.77–0.94, n = 113, R² = 23.1).

Discussion

In this study, we found that most individuals with self-reported stroke failed to fulfil criteria for MCI, including aMCI, nMCI or mMCI, mainly due to restrictions on functional ability. In individuals who reported a history of stroke, the best predictors for 2-year incident dementia were SMC and scores on the CAMCOG sub-domains of learning memory and praxis.

In CFAS, health status was self-reported and therefore disease prevalence estimates may reflect bias in memory or awareness of a condition. However, it should be noted that self-reported and objective disease status has previously been found to be in high agreement for the diseases included in this analysis [18, 19]. Further, brain imaging was not available and we are therefore unable to determine the prevalence of silent strokes, and whether features of stroke such as locality or sub-type (e.g. haemorrhage or infarct) influence cognitive profiles and risk of dementia. MCI was defined using Mayo Clinic criteria [5] for aMCI and criteria for nMCI and mMCI [6]. More inclusive definitions of MCI that cover a broader range of cognitive (e.g. executive deficits and deficits in global cognitive functioning) and functional deficits, such as the definition of cognitive impairment no dementia (CIND) [20], may be more useful for capturing cognitive impairment in the context of stroke. However, we tested the sensitivity of different MCI sub-types, including aMCI, nMCI and mMCI. This had little effect on the estimated prevalence. Further, MCI criteria were never designed to be used within the context of stroke and, as suggested by the results, alternative methods are needed to capture VCIND associated with stroke. Additional risk modelling was also undertaken to avoid the limitations of attempting to fit predefined criteria...
that were not developed nor validated for dementia prediction in the context of vascular disease.

It was found that current criteria for MCI are not the best approximation for cognitive impairment following stroke. Individuals with stroke appear to have a more extreme pattern of impairment that falls outside the MCI range. Their cognitive profile reflects impairment in global function, memory and non-memory domains. Therefore, definitions that rely only on poor memory or non-memory performance will be too restrictive. Further, a high proportion of stroke cases had severe functional impairment and this is typically an exclusion when diagnosing MCI across the many different definitions [13]. If a pre-dementia state is to be mapped within the framework of stroke, a broader concept than MCI is needed.

Results from the risk factor analysis suggest that impairments in domain-specific cognitive scores, including non-memory (e.g. praxis) and memory (e.g. learning memory) combined with SMC (self or informant), predict 2-year dementia progression best in stroke cases. These results support recent findings highlighting the importance of poor cognitive function in predicting dementia in the context of stroke [3, 21–24] extending them to suggest that only limited domains need to be tested, but tests of memory and non-memory performance should be included. Few variables may be needed to predict dementia in stroke cases as stroke itself already confers a high risk for dementia [1]. Indeed, demographic factors (including age and education), lifestyle variables (e.g. alcohol use and smoking), mental health (e.g. depression and anxiety) and disease co-morbidity were also not found to be predictive of incident dementia in stroke cases. Health-related co-morbidity has been previously associated with higher risk of dementia in stroke cases in some (over 8-year follow-up) [21], but not all studies [5, 25]. In a recent review [1], recurrent stroke rather than cardiovascular risk factors was found to be associated with dementia. Determining cases where disease co-morbidity is associated with greater risk of dementia has important implications for treatment. Further studies investigating whether other variables associated with dementia [e.g. genetics such as apolipoprotein (APOE) e4 status] improve dementia risk prediction in stroke cases and whether MRI derived-stroke-related factors (e.g. such as laterality, sub-type) mediate risk prediction are needed.

Health-related co-morbidity has been previously associated with higher risk of dementia in stroke cases in some (over 8-year follow-up) [21], but not all studies [5, 25]. In a recent review [1], recurrent stroke rather than cardiovascular risk factors was found to be associated with dementia. Determining cases where disease co-morbidity is associated with greater risk of dementia has important implications for treatment. Further studies investigating whether other variables associated with dementia [e.g. genetics such as apolipoprotein (APOE) e4 status] improve dementia risk prediction in stroke cases and whether MRI derived-stroke-related factors (e.g. such as laterality, sub-type) mediate risk prediction are needed.

Conclusion

How do these results help in defining those individuals with stroke at increased risk of dementia? The results suggest that criteria for VCIND should include both subjective and objective cognitive function, not exclusively focused on non-memory performance. Prediction of who will develop cognitive impairment and dementia in individuals with stroke is a major challenge. This has important clinical implications and may allow for better estimation of prognosis, and improved care and future planning for stroke patients. Future studies need to determine whether cognitive or other interventions in people with stroke reduce dementia risk.

Key points

- VCIND is an umbrella term that captures cognitive deficits associated with vascular disease that falls short of a dementia diagnosis.
- Identification of VCIND is a major challenge due to a lack of operational criteria.
- The question of the validity of MCI outside of Alzheimer's disease is timely and important.
- MCI criteria fail to capture cognitive impairment and risk of dementia in the context of stroke.
- In stroke cases, SMC and objective cognitive performance (memory and non-memory) predict dementia and these variables could possibly be incorporated into criteria for VCIND.

Author contributions

B.C.M.S. contributed to design, analysed the data, drafted the first version of the manuscript and was responsible for revisions. T.M. and G.M. contributed to design and analysis and revised the manuscript. F.M. provided intellectual input into the manuscript. C.B. is the PI of the CFAS study and contributed to design and editing of the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

None declared.

Ethical approval

CFAS was approved by the local ethics committee and has multicenter ethics committee approval (ethics approval reference 05/mrec05/37).

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