Vascular disease and cognitive function in older men in the Caerphilly cohort

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Abstract

Objectives: stroke can impair cognitive function, but the associations between other manifestations of vascular disease and cognitive function have not been adequately studied in representative population samples of subjects. We report the associations between cardiac and peripheral vascular disease and cognitive function for a large representative sample of men in Caerphilly, South Wales, UK.

Design: the Caerphilly cohort is the basis of on-going studies of vascular disease, of cognitive function and of predictors of these. We have made intensive attempts to identify all cases of vascular disease: myocardial infarction, angina, ECG ischaemia, peripheral vascular disease (intermittent claudication) and stroke. Here we present data on associations between vascular disease and cognitive function.

Setting: the study is based upon a representative population sample of over 1,500 men in South Wales, aged 55–69 years when cognitive function was measured. The men, and hospital and GP notes relating to them, had been repeatedly examined for evidence of vascular disease during the previous ten years.

Main outcome measures: standard tests of cognitive function: the AH4, CAMCOG, MMSE and choice reaction time.

Results: After the omission of men who had had a stroke, we detected significant associations between cognitive function and the presence of angina, ECG ischaemia, past myocardial infarction and intermittent claudication. The strength of the associations between cognitive function and the various manifestations of vascular disease were similar, and the various cognitive function tests showed effects of similar size. Overall, cardiac and peripheral vascular disease is associated with a significant reduction in cognitive function equivalent to about one sixth of the standard deviation of a number of tests of cognitive function. The size of this effect is roughly equivalent to the decline in cognitive performance over five years of ageing.

Conclusions: subjects with evidence of cardiac or peripheral vascular disease have on average a significant reduction in cognitive function equivalent to about four or five years of additional age. The effect of long-term, low-dose aspirin on cognitive decline should now be tested.

Keywords: angina, cardiovascular disease, intermittent claudication cognitive function, myocardial infarction, reaction time

Introduction

Vascular diseases are the second most common cause of cognitive decline and dementia [1, 2]. Stroke can have a massive effect on cognitive function, and dementia is a common outcome of stroke [3–5]. ‘Multi-infarct dementia’ or ‘vascular dementia’ are terms used to describe cognitive deterioration which is assumed to be due to progressive occlusion of cerebral arteries and loss of cerebral tissue.

The association between cognitive function and vascular disease other than cerebral, such as heart disease or peripheral arterial disease, has been little studied and some of the published reports are based on highly selected groups of patients [5, 6] or on volunteers [7, 8]. Most studies, however, report associations between the different manifestations of vascular disease and cognitive function [8–14], though a few fail to find an association [15, 16]. One claims an association in women but not in men [17].
The Caerphilly cohort is a large representative sample of men in South Wales [18] the members of which have been studied intensively for the past 20 years. A major objective has been to examine a wide range of possible predictors of myocardial infarction and stroke. In the second re-examination of the men, estimates were made of cognitive function. In this report we assess the strength of the associations between cognitive function and various manifestations of cardiac and peripheral vascular disease.

Methods

The Caerphilly Study was set up in 1979–83, the primary aim being the study of life-style, dietary, biochemical and haemostatic factors predictive of ischaemic heart disease [18]. The men have since been re-examined at four to five year intervals. In the Phase III examinations, when the men were aged 55–69 years, cognitive function was added to the investigations [19].

Special afternoon and evening clinics were held for a general examination at which questions were asked about lifestyle, past illnesses and general state of health. Current occupation or most recent job was used as a basis for social class classification. Medical history and clinical details relevant to vascular disease were recorded, together with a chest and limb lead ECG. The men were then asked to attend an early morning clinic after an overnight fast, at which a blood sample was taken.

Soon after this, a specially trained technician saw each man at home and tests of cognitive function were done [19]. The order of the tests and the method of application was rigidly standardized and a laptop computer was used for some of the tests.

Disease states

We used standard diagnostic criteria for the definition of vascular disease. Each man was asked about admission to hospital and about symptoms of possible strokes. The London School of Hygiene and Tropical Medicine questionnaire on chest pain and possible intermittent claudication [20] was administered. Information from all these, together with admission lists from all the local hospitals were the basis of a search of hospital and GP notes for possible vascular disease events. Standard criteria were applied to identify myocardial infarction (MI), angina, intermittent claudication and stroke [21, 22]. For ECG ischaemia, we interpreted the presence of major or moderate Q waves as being indicative of 'probable' ischaemia.

The tests of cognitive function

The tests used were of general reasoning and speed of reaction have been fully described elsewhere [19].

Results

The tests of cognitive function and the methods of their administrations are described elsewhere [26]. The tests of cognitive function are all highly correlated (for all possible pairs: \( P < 0.001 \)). The coefficients suggest, however, that while there is considerable overlap between the AH4 and the CAMCOG (\( r = 0.69 \)) and between both these and the MMSE (\( r = 0.57 \) and 0.74), the choice reaction time test yields data that are more independent (for the AH4, CAMCOG and MMSE \( r \) is \(-0.42, \ -0.38 \) and \(-0.27 \) respectively).

The total available sample comprised 2,154 men aged 55–69 years. Of these 1,870 (87%) agreed to cognitive testing but the results for some men (between 17 and 167 for the different tests) were omitted because the tests were judged not to have been completed satisfactorily. Fifty-one men were excluded because of a previous stroke and 26 men who had had other cerebral events were also excluded. Satisfactory data for the tests
and adequate data on the confounding factors are available for around 1,700 men.

About 1,100 men had no clinical evidence of any vascular disease. The numbers for whom there was clinical evidence of the various manifestations of vascular disease, and for whom complete data are available, are shown in the table. These numbers are not mutually exclusive, and overall, 447 men had evidence of ischaemic heart disease (IHD) and 461 of vascular disease other than stroke. This group of 461 men does not include 192 men with ‘possible’ ECG ischaemia, but these are included in the ECG ischaemia group.

The table shows the mean levels of the various cognitive function tests in the men with no vascular disease and the differences between these and the mean scores in sub-groups of men defined by the various diseases. These differences have been adjusted to allow for the effects of age and social class and each difference is shown as a proportion of the SD for that test. This enables valid comparisons of effects to be made across the tests, despite the various measurements being in different units. There is no significant interaction with age. Though the addition to the model of mood [25] at the time of testing reduces the sizes of the associations slightly, most of the associations remain statistically significant.

The sizes of the effects are similar (see Table 1). None of the differences between the scores for the tests within any of the diagnostic sub-group achieves statistical significance at $P<0.05$. Although angina, and perhaps intermittent claudication, may appear to be associated with a poorer performance on some of the tests, the differences are similar in size and statistically homogeneous with the scores in the other diagnostic groups. Thus the best estimate of the effect of any manifestations of vascular disease is obtained from the total group of men with any manifestation of vascular disease. In terms of the proportion of the relevant SD, these effects represent decrements in the men with vascular disease of 16% for the AH4, 13% for the MMSE, 14% for the CAMCOG and 18% for the choice reaction time.

Another way of interpreting these effects is to compare the differences with the decline attributable to ageing. That is, if the decrements in the scores of men with vascular disease (in comparison with the men without disease) are compared with the effects of age alone—independent of the effects of social class and vascular disease—then vascular disease appears to have an effect equivalent to five years of ageing for the AH4 and 4 years of ageing for the CAMCOG, the MMSE and the CRT.

Furthermore, the associations of vascular disease with the different tests are of similar strengths and statistically homogeneous, and so the whole table can reasonably be summarized by a single figure. That is, men with prevalent vascular disease (other than symptomatic stroke) have on average a cognitive performance lower than that of men with no evidence of any vascular disease by about one sixth, or 16% of the SDs for any of the tests. In terms of the decline with ageing, this is equivalent to between four and five years of additional age.

Discussion

The effect of stroke on cognitive performance can be massive, causing dementia in some patients [3, 4]. We have chosen to omit men with known stroke from this report because those most severely affected would have been unable to do the tests. Moreover, whatever results we might have obtained would relate to a biased population sample. Cerebral episodes of lesser severity may not be diagnosed, unless they are progressive and lead to a diagnosis of ‘multi-infarct’ or ‘vascular’ dementia. Prevalence rates for this condition are uncertain, but vascular causes probably explain about a quarter or a third of cases of dementia in the UK [1, 2].

While cerebro-vascular disease can go unrecognized, vascular disease in the coronary and peripheral circulation is more easily identified. It may therefore constitute a ‘marker’ for cerebro-vascular disease, and hence for early, pre-symptomatic cognitive decline. The results we present support this view.

The Caerphilly study is based on a large representative population sample of older men. Representativeness has been compromised by the omission of a few men who refused to complete the cognitive function tests and a few others who were unable to do the tests. Men known to have had a stroke were not included. Therefore, although the Caerphilly cohort has been subjected to relatively little selection, these omissions will have led to the full effects of vascular disease (other than stroke) being underestimated.

The similarity in the sizes of the effects of the various manifestations of vascular disease, and the similarity in the differences shown by the various cognitive function tests, enables us to say that men with clinical evidence of vascular disease, other than stroke, showed a decrement of about one-sixth of a SD in their cognitive performance, independent of the effects of age and social class.

A possible confounding factor that may account for some of this decrement is depression, and we do find that scores on the General Health Questionnaire (GHQ) [25] (an indirect measure of depression) are significantly related to the presence of angina—though not to other manifestations of vascular disease [27]. When we add scores for the GHQ to the present model, all the relationships shown in Table 1 are attenuated by about a third, but the associations with MMSE and the choice reaction time remain significant. However, we believe that the inclusion of depression in the model leads to over-correction, on the grounds that depression is...
Table 1. Numbers of men in the cohort with no evidence of vascular disease and their mean (SD) cognitive function scores. Differences, adjusted for the effects of age and social class, are then shown between these scores and the mean scores within groups of men with various manifestations of cardiac and peripheral disease. These differences are also shown as proportions of the SD for that test.

<table>
<thead>
<tr>
<th></th>
<th>No vascular diseasea number of men</th>
<th>mean (SD)</th>
<th>MMSE score</th>
<th>CAMCOG score</th>
<th>Choice reaction time m sec</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AH4 score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI number of men</td>
<td>235</td>
<td>26.7 (10.6)</td>
<td>1048</td>
<td>1102</td>
<td>1098</td>
</tr>
<tr>
<td>differenceb 95% CI</td>
<td>−1.31 (12% SD)</td>
<td>−0.11 (5% SD)</td>
<td>−0.54 (8% SD)</td>
<td>+51 (21% SD)</td>
<td>224</td>
</tr>
<tr>
<td>ECG ischaemia number of men</td>
<td>336</td>
<td>1.05 (10% SD)</td>
<td>−0.34 (15% SD)</td>
<td>−0.92 (14% SD)</td>
<td>+14 (6% SD)</td>
</tr>
<tr>
<td>differenceb 95% CI</td>
<td>−2.56 to −0.05</td>
<td>−0.41 to 0.20</td>
<td>−1.30 to 0.33</td>
<td>15 to 85</td>
<td></td>
</tr>
<tr>
<td>Angina number of men</td>
<td>267</td>
<td>−2.18 (21% SD)</td>
<td>−0.44 (19% SD)</td>
<td>−1.01 (16% SD)</td>
<td>+32 (13% SD)</td>
</tr>
<tr>
<td>differenceb 95% CI</td>
<td>−3.41 to −0.93</td>
<td>−0.73 to −0.15</td>
<td>−1.77 to −0.15</td>
<td>−1 to 43</td>
<td></td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>34</td>
<td>−1.11 (10% SD)</td>
<td>−0.48 (21% SD)</td>
<td>−1.82 (28% SD)</td>
<td>+56 (23% SD)</td>
</tr>
<tr>
<td>number of men differenceb</td>
<td>4.29 to 2.08</td>
<td>−1.21 to 0.24</td>
<td>−3.75 to 0.15</td>
<td>−27 to 140</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>422</td>
<td>447</td>
<td>447</td>
<td>405</td>
<td></td>
</tr>
<tr>
<td>Any ischaemic heart disease</td>
<td>−1.71 (16% SD)</td>
<td>−0.31 (13% SD)</td>
<td>−0.91 (14% SD)</td>
<td>+42 (17% SD)</td>
<td>12 to 69</td>
</tr>
<tr>
<td>number of men differenceb</td>
<td>−2.69 to −0.62</td>
<td>−0.53 to −0.03</td>
<td>−1.48 to −0.17</td>
<td>15 to 71</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>434</td>
<td>461</td>
<td>461</td>
<td>416</td>
<td></td>
</tr>
<tr>
<td>Any vascular disease number</td>
<td>−1.76 (17% SD)</td>
<td>−0.33 (14% SD)</td>
<td>−0.99 (15% SD)</td>
<td>+44 (18% SD)</td>
<td>15 to 71</td>
</tr>
<tr>
<td>of men differenceb</td>
<td>−2.74 to 0.69</td>
<td>−0.55 to −0.06</td>
<td>−1.57 to −0.25</td>
<td>15 to 71</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

aMen with previous stroke have been omitted throughout.

bDifferences from men with no evidence of vascular disease are adjusted for age and social class.
probably more likely to be an outcome of a failing cognitive performance than a factor truly confounding relationships with vascular disease.

There have been few similar studies published on this topic and some of these have been small or based on highly selected groups of patients. For example, van Boxtel et al. [8] reported results for 1,360 subjects, aged 24–81 years, who were volunteers out of a total panel of over eight thousand subjects. The conclusion drawn from this selected group was that chronic diseases, of which vascular disease was only a part, contribute only about 3.5% to the variance in cognitive function. This is close to our estimate.

Breteler et al. [9] applied the MMSE to a representative population sample of 4,971 subjects aged 55–94 years. After standardisation for age, sex and education, they found a reduction in score of 0.7 and 0.8 in subjects with ECG evidence of myocardial infarction and symptoms of peripheral arterial disease. These differences are larger than our estimates (0.3 and 0.5 respectively).

A study of the speed of response by 61 pairs of twins showed an increase in the subjects who reported cardiovascular disease of 35 m sec [10]. This is close to the 44 m sec in our cohort for the test which involved choice.

Launer et al. [11] examined the decline in MMSE score over three years in 489 men in the Zutphen cohort. Men with vascular disease showed a significantly larger decline than those without evidence of vascular disease, but patients who had had a stroke were retained in the group. In a later report [13], however, they state that the subjects who had coronary artery disease together with the ApoE4 allele had a substantially increased risk of dementia (OR 6.1; 95% CI 1.7–22.3).

An early report from the Honolulu Heart Program, based on a representative sample of 3,734 Japanese-American men, gave no convincing evidence of an association between cognitive function and a history of myocardial infarction or coronary artery by-pass graft [16]. A later report from this cohort [14] showed, however, that within a sub-group of 45 men with vascular dementia the odds ratio for coronary heart disease was 1.50 (95% CI 1.35–4.62) when compared with 2,871 men who had neither dementia or stroke, indicating that within selected subjects coronary heart disease can be a strong predictor of vascular dementia.

Two studies failed to find evidence of any association. A study of ‘very old people’ followed for three years found an odds ratio for the development of dementia in 240 subjects with coronary heart disease during a three year follow up of 1.0 (95% CI 0.7–1.5), compared to 684 subjects with no such evidence [17]. No association was found in 157 men aged 75–85 years in the Bronx Aging Study, though curiously they reported a five-fold increase in dementia in 285 women with a history of myocardial infarction [15].

In summary, the association between cardiac and peripheral vascular disease and cognitive function appears to be important, though relatively small. In our cohort about 16% of the standard deviation of a range of tests can be explained statistically by the presence of vascular disease other than symptomatic stroke. A decline of this size is equivalent to four or five years of ageing. This estimate appears to be similar to those reported in other studies. Because of omissions of the most severely affected men in every study, these estimates underestimate the full effects of vascular disease.

Cardiac and peripheral vascular disease are only surrogate indicators of disease in the cerebral circulation. They are also markers of patients at increased risk of multi-infarct dementia [28]. Long-term aspirin and other anti-thrombotic prophylactic interventions, in addition to directly reducing the incidence of strokes, might delay cognitive decline and the onset of dementia. Evidence of benefit from aspirin in this context has already been suggested in one trial [29] and evidence from further randomized controlled trials is now required.

Key points

- Subjects with evidence of cardiovascular disease, but no stroke, show on average a deficit in cognitive function similar in size to the decline during about five years of ageing.
- The size of the deficit is similar in men with evidence of previous myocardial infarction, cardiac ischaemic and peripheral vascular disease.
- The proportionate size of the deficit is similar in tests which evaluate different cognitive functions.

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References


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