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Homocysteine and post-stroke cognitive decline

Sir—Normal fasting total plasma homocysteine (tHcy) concentrations range from 5 to 15 \(\text{µmol} \text{l}^{-1}\) [1, 2]. Hyperhomocysteinaemia has been classified as moderate, intermediate or severe if levels are 15–30, >30–100 or >100 \(\text{µmol} \text{l}^{-1}\), respectively [3]. Whereas severe hyperhomocysteinaemia is uncommon, moderate levels can exist in healthy controls [4]. Hyperhomocysteinaemia has been associated with risk of stroke, myocardial infarction (MI) [5], Alzheimer’s disease (AD) [6] and vascular dementia [7]. Studies of cognitive decline and tHcy in healthy controls, however, conflict [8, 9]. Vascular disease patients may have higher tHcy than AD patients [10], thus, hyperhomocysteinaemia in demented subjects [7] could be due to concomitant vascular disease, rather than a cause of dementia. This, however, is controversial since elevated tHcy has existed in pathologically confirmed AD cases both with and without vascular disease as well as in vascular dementia [11].

How hyperhomocysteinaemia promotes dementia is unknown, although mechanisms are proposed [12, 13] which may explain co-occurrence with vascular disease, stroke and AD.

Sixty per cent of non-demented stroke subjects had tHcy ≥15 \(\text{µmol} \text{l}^{-1}\) and higher levels were related to attentional and executive function deficits [4]. This leads us to hypothesise that stroke patients with hyperhomocysteinaemia should be pre-disposed to dementia. Our objective was to investigate whether tHcy at 3 months post-stroke predicted cognitive outcome in elderly, well recovered, non-demented subjects. We examined whether tHcy associated with incidence of dementia/general cognitive decline or changes in attention, language expression and executive function over 2 years.

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References


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Methods

Approval was granted by local research ethics committees. Three hundred and fifty-four patients gave written informed consent (with assent from next-of-kin where available) to clinical and neuropsychological investigations. tHcy was measured using standard techniques [14] in 170 subjects giving additional consent for blood sampling at 3 months post-stroke.

Hospital notes were reviewed for pre-stroke hypertension, atrial fibrillation (AF), MI, hypercholestraemia and diabetes. Clinical and CT scan evidence-based diagnoses of stroke, Oxford Community Stroke Project (OCSP) classification [13] and smoking and alcohol habits were recorded. One hundred and fifty-four subjects (90.6%) had ischaemic infarctions, 2 (1.2%) haemorrhagic infarctions, 2 (1.2%) intracerebral haemorrhages and 4 (2.4%) exhibited transient ischaemic attacks. Of those with ischaemic infarctions, 8 (5.2%) had total anterior circulation infarcts (TACI), 65 (42.2%) had partial anterior circulation infarcts (PACI), 56 (36.4%) exhibited lacunar infarcts (LACI) and 24 (15.6%) showed posterior circulation infarcts (POCI).

The CAMCOG [16] and Cognitive Drug Research computerised battery [17] were performed at 3, 15 and 27 months post-stroke. Incident dementia was diagnosed using DSMIV criteria. ‘Decliners’ were defined as those who attained the primary outcome (dementia or a CAMCOG score below 80) at 27 months. Secondary outcomes were attained the primary outcome (dementia or a CAMCOG score using DSMIV criteria). ‘Decliners’ were defined as those who showed posterior circulation infarcts (POCI).

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Results

Although the 170 participants with tHcy measures were similar to those for whom tHcy was not measured in age and gender, they differed in mean baseline CAMCOG scores (87 versus 84 respectively: \( P = 0.002 \), logistic regression).

Characteristics of participants are summarised in Appendix 2 on the website (http://www.ageing.oxfordjournals.org). Eighty-seven of the 170 participants (51.2%) had hyperhomocysteinaemia (tHcy (25) > 15 \( \mu \)mol l\(^{-1} \)); 99% of these were between 15 and 30 \( \mu \)mol l\(^{-1} \). There was a higher prevalence of MI in the upper homocysteine quartile (\( P \) from Chi-squared comparing tHcy quartiles = 0.020). Lower levels of vitamin B12 and RCF and higher levels of creatinine associated with higher levels of homocysteine (\( P \) from one-way ANOVA comparing quartiles = 0.011, <0.001 and <0.001 respectively). Since 11 participants were awaiting re-assessment at 27 months, 21 withdrew and 12 died, the cohort was left with 126 for the primary outcome analysis. These 126 patients were similar to the 44 not re-assessed in relation to age, gender, homocysteine level (\( P \)-values from logistic regression = 0.361, 0.413, 0.655, respectively), and in terms of evidence-based diagnoses of stroke (\( P \)-value from Chi-squared = 0.508). There was, however, a difference in baseline CAMCOG score between those assessed and not assessed at 27 months (logistic regression \( P \)-values = 0.048: mean CAMCOG = 87 and 85 respectively).

Table 1 shows cognitive changes across homocysteine quartiles. One hundred subjects did not attain decliner status at 27 months. Sixteen of the 26 decliners had dementia. There was no significant difference between decliners and non-decliners in terms of stroke type; decliners had ischaemic infarctions: 8% TACI, 48% PACI, 36% LACI, 8% POCI. Neither homocysteine level nor any confounders were significantly associated with cognitive decline or changes in secondary cognitive outcomes over 27 months (Table 2).

Discussion

Our cohort comprised Caucasian, well-recovered elderly patients. In contrast to a younger multi-ethnic cohort in south London [19] that may explain differences in the outcomes with respect to infarction sub-types; we noted

<table>
<thead>
<tr>
<th>Table 1. Changes in cognitive performance between 3 and 27 months post-stroke</th>
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<tr>
<td>Subjects assessed at 27 months</td>
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<tr>
<td>-------------------------------</td>
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<tr>
<td>Total number of cases</td>
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<tr>
<td>Number with cognitive decline&lt;sup&gt;a&lt;/sup&gt; by 27 months</td>
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<tr>
<td>Mean change (SD) in&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Total CAMCOG score</td>
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<td>Executive function</td>
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<td>Language expression</td>
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<td>PoA (sec)&lt;sup&gt;b&lt;/sup&gt;</td>
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<sup>a</sup> Cognitive decline was defined as a diagnosis of dementia or a total CAMCOG score of less than 80 at 27 months.

<sup>b</sup> Change was calculated by baseline minus 27 month scores; for total CAMCOG score, language expression and executive function, negative numbers represent an improvement. For PoA, negative numbers indicate a decline. CAMCOG and PoA data were available for 117 and 109 subjects respectively at 27 months.
in more detail and demonstrated a mean level of 11 on participants in the VISP Trial examined the acute phase to around 10 homocysteine levels of 8 to 9 levels change following stroke. In one study, acute phase may no longer be the case. It is unclear how homocysteine to 6 months. However, once this period has passed, it is plausible that early homocysteine measurement is sampling times, assessment intervals and ages of participants. Contrasting results could be due to different homocysteine contrasting results could be due to different homocysteine stroke recovery response reflect long-term tHcy elevations. Further studies will need to address this.

Our trend for increased prevalence of MI with increasing homocysteine concentrations agrees with others [5]. The trend for lower levels of vitamin B12 and RCF with higher tHcy is consistent with their roles in homocysteine metabolism.

Our lack of association between homocysteine and cognitive decline could be explained by methodology. Our sample size, although comparable to the Sydney Stroke study (with Odds Ratio of 3.27) [4], may still be inadequate for detecting longitudinal decline. There was additional sampling bias because those patients for whom we obtained tHcy were less impaired than those for whom we did not; more impaired patients are less inclined to undergo additional investigations. Losses to follow up increased the potential for residual confounding further as did the exclusion of aphasic or severely disabled subjects or those developing dementia within 3 months of stroke. Homocysteine was measured once only. Whilst this is accepted practice, it is reasonable to propose repeated measurements to compare dynamic changes in homocysteine [20, 21] with cognitive changes. Length of exposure to elevated homocysteine may be important in determining cognitive effect [22], how well single measures reflect this is unknown. Finally, our relatively homogeneous homo cysteine levels may not have provided enough variability to detect associations within 27 months; longer follow up may be appropriate.

There is still debate about the feasibility of improving outcome for cardiovascular patients by modulating tHcy. Although the VISP study did not demonstrate overall efficacy for folate and vitamin B administration following stroke, a retrospective sub-analysis suggested that higher B12 doses may be more appropriate [23]. The NORVIT study [24] similarly, did not reduce risk of recurrent cardiovascular disease following MI. Another trial whilst demonstrating a homocysteine lowering effect of folate and B vitamin therapy did not demonstrate concurrent improvement in cognitive function in healthy elderly subjects over 2 years [25]. Our question about whether there is an association between elevated homocysteine levels and post-stroke cognitive impairment/dementia is, nevertheless, important. Clearly if there is no proven causal relationship between tHcy and cognitive impairment, tHcy lowering strategies will not serve to reduce dementia incidence and other mechanisms will need to be investigated. However, if there is a causal relationship,
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further modification of current folate/vitamin B treatment regimens may be necessary.

In summary, single post-stroke homocysteine measurements did not predict dementia or cognitive decline at 27 months post-stroke in well-recovered elderly subjects.

Key points

- Fifty-one per cent of elderly non-demented stroke patients have hyperhomocysteinaemia at 3 months post-stroke.
- Seventy-nine per cent of elderly stroke patients scored above 80 points on the CAMCOG at 27 months post-stroke.

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Conflicts of Interest Declaration

There are no conflicts of interest.

References


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