Abstract

Objective: to report on the relationship between serum folate levels and the prevalence of stroke, peripheral vascular disease, cognitive problems and short-term mortality in elderly people.

Setting and participants: 1171 subjects whose serum folate was determined as part of their clinical examination in the Canadian Study of Health and Aging, a population study of individuals 65 years and older.

Methods: cross-sectional analysis compared relationships between serum folate levels and clinical features; longitudinal analysis examined mortality at follow-up by folate status at the time of the clinical examination.

Results: membership in the lowest quartile for serum folate was associated with an increased likelihood of stroke. Those with low folate levels were more likely to be demented, institutionalized and depressed. In the cognitively impaired but not demented group, those with low folate levels scored lower on the Modified Mini Mental State and had more short-term memory problems.

Conclusions: low folate level was a significant explanatory variable for stroke. Low folate levels were common in all types of dementia and were associated with a history of weight loss, lower body mass index and lower serum albumin concentrations. This may reflect the reduced ability of cognitively impaired individuals to eat adequately.

Keywords: cognition, elderly people, serum folate, stroke

Introduction

The finding that folate deficiency at a cellular level can occur even with 'normal' serum folate values [1–3] implies that many people are potentially affected by this deficiency. The association between low serum folate levels and megaloblastic anaemia is well known [4, 5]. Low folate levels are also associated with vascular disease. This relationship may be explained by elevated homocysteine levels: folate is a cofactor for homocysteine metabolism and individuals with low folate levels have increased serum homocysteine concentrations [6]. Even folate levels that are in the low normal range may not prevent elevations of homocysteine [1]. Elevated concentrations of serum homocysteine increase the risk of vascular disease [7–11], independent of other risk factors for vascular disease [12].

One study has directly examined the relationship between serum folate and vascular disease. The relative risk for ischaemic stroke in those with a serum folate level less than 9.3 nmol/l was 1.37 [13]. The effectiveness of folic acid supplementation in reducing elevated homocysteine [14, 15] suggests that consumption of this vitamin may be effective in reducing vascular risk.

The primary objective of our study was to determine whether an association existed between low serum folate levels and the prevalence of stroke, peripheral vascular disease, or short-term (2-year) mortality in a subset of participants of the Canadian Study of Health and Aging (CSHA). A secondary objective was to examine the relationship between folate levels and the various types of cognitive impairment found in elderly people. We hypothesized that vascular cognitive impairment [16] would occur most commonly in subjects with low folate levels.

Methods

The CSHA was a national study designed to examine different aspects of ageing in Canadians 65 years and older. Eighteen urban study sites from all 10 provinces participated, with equal representation from each of the country's five regions [17]. Each centre obtained ethical approval from its institutional review board. The community sample was randomly selected from
the databases of provincial health insurance plans in all areas except Ontario, where subjects were randomly selected from electoral and municipal records. Older age groups were intentionally over-sampled using an optimal allocation technique.

Subjects
For community subjects the study had two phases. Subjects underwent a standardized interview during which cognition was assessed with the Modified Mini Mental State (3MS) examination [18]. Community subjects scoring less than 78, those who could not be screened, all institutional subjects and a random selection of community subjects who scored above 77 went on to a detailed clinical assessment. As part of the community survey, subjects were asked about their self-rated health (‘Would you say your health is very good, pretty good, not too good or poor or very poor?’). Data were collected in 1991–92.

Clinical assessment
The clinical assessment was to determine if dementia was present and to make an aetiological diagnosis. The assessment, described in detail elsewhere [17], included a standardized medical history, an informant interview, a physical and neurological examination, neuropsychological testing (if the 3MS score was above 50) and selected laboratory tests (including serum folate and albumin concentrations). Neuropsychological testing assessed memory, abstract thinking, judgement, constructional abilities, language and object recognition [19]. We used the neuropsychologist’s final determination of whether deficits existed in these areas for our analysis.

Participants and/or informants were specifically asked about hypertension, diabetes mellitus, smoking and a family history of cerebrovascular disease. Clinicians noted whether subjects had had intermittent claudication or strokes. Clinicians were asked to report whether subjects had ‘cardiac symptoms’ but not to distinguish between specific cardiac problems (e.g. ischaemic heart disease or atrial fibrillation). A list of all current medications was obtained. The physical examination included blood pressure assessment, notation of pulse abnormalities and a search for focal neurological signs. A Hachinski ischaemic scale was completed on examined subjects [20]. Neuro-imaging was not performed. The investigators did not have access to health records.

Our determination of stroke was based on the opinion of the examining physician. We felt that the accuracy of this would be equivalent to, if not greater than, self-reporting (as compared with a detailed review of all health records) [21–23]. The validity of clinical determination of stroke is supported by the higher mean Hachinski scores for subjects stated to have such a history (8.38 versus 2.28; P < 0.001).

At the completion of the assessment, subjects were categorized as having no cognitive loss, being cognitively impaired but not demented (CIND) or being demented (using American Psychiatric Association. Diagnostic and Statistics Manual of Mental Disorders, 3rd edition, revised, criteria) [24]. Demented subjects were further categorized as to the likely cause (Alzheimer’s disease [25], vascular dementia [26], other types of dementia or unclassified dementia). Subjects with vascular cognitive impairment were those judged to have impaired cognition on the basis of vascular insult(s). This grouping included subjects categorized as having vascular dementia, possible Alzheimer’s disease with cerebrovascular disease and CIND from a vascular cause [16].

Participation rates (the proportion of those invited for a clinical assessment who agreed to attend) were 77% in the Atlantic region, 75.4% in Ontario, 74.6% in Quebec, 68.1% in British Columbia and 66.7% in the Prairies region. Clinical assessments were completed on 2914 subjects but not all of these agreed to venepuncture. Serum folate levels were measured in 1409 subjects: these individuals were more likely to be institutionalized (49.3% versus 37.2%; P < 0.006), have lower mean 3MS scores (56.8 versus 66.0; P < 0.006) and be demented (52.1% versus 26.3%; P < 0.0006). We examined the frequency of anticonvulsant use, alcohol use and smoking because of their reported influence on folate levels [27–30].

Follow-up data
The primary purpose of the longitudinal component of our study was to determine whether there was an association between serum folate levels and the likelihood of dying by the time of a follow-up telephone survey carried out in 1993. This re-contact with study participants who had been living in the community, provided survival status and responses to a number of health-related questions. Subjects were not asked whether they had had a stroke since the time of first contact. Data were obtained either from the subject or a proxy. Cause of death was not recorded.

Analysis
The database available to us did not identify subjects by study centre. Fifteen sites agreed to participate in this secondary analysis by allowing identification of their centre’s data (final number of subjects = 1171). Subjects in the participating centres were significantly older (81.3 versus 79.5; P < 0.007), more likely to be institutionalized (44.3% versus 37.9%; P < 0.04) and more likely to have dementia (40.8% versus 30.7%; P < 0.0007) than subjects from the three non-participating sites. Subjects in the non-participating centres were more likely to be French-Canadian (68.8% versus 11.8%; P < 0.0001).
Folate in elderly Canadians

Table 1. Canadian Study of Health and Aging (1991–92): differences between subjects in the lowest (Q1) and highest (Q4) quartiles

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Q1 (n = 328)</th>
<th>Q4 (n = 265)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>81.5 ± 7.5</td>
<td>81.3 ± 7.3</td>
<td>0.75</td>
</tr>
<tr>
<td>Institutional residence (%)</td>
<td>57.9%</td>
<td>41.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Demented (%)</td>
<td>64.6%</td>
<td>45.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Depressed (%)</td>
<td>40.0%</td>
<td>40.0%</td>
<td>0.003</td>
</tr>
<tr>
<td>With history of weight loss (%)</td>
<td>17.3%</td>
<td>8.9%</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean serum albumin concentration (g/l)</td>
<td>37.7</td>
<td>38.8</td>
<td>0.005</td>
</tr>
<tr>
<td>With positive self-rated health (%)</td>
<td>67.0%</td>
<td>82.3%</td>
<td>0.013</td>
</tr>
<tr>
<td>Mortality at follow-up (%)</td>
<td>31.4%</td>
<td>25.3%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Since the CSHA used no central laboratory, ranges for normal folate values varied between the 15 centres. We categorized serum folate values into quartiles with respect to all the values obtained from that subject’s study centre using MINITAB statistical software. The maximum values for the lowest quartile ranged from 7 to 10 nmol/l, while the minimum values for the highest quartile ranged from 14 to 26 nmol/l.

Descriptive statistics, Student’s t-tests and χ2 analyses were performed as indicated. For most analyses we compared the lowest folate quartile (Q1) with the highest quartile (Q4). Stepwise logistic regression (BMDP Statistical software, Los Angeles, CA, USA) was used to determine significant explanatory variables for history of stroke and mortality. Age, gender, history of arterial hypertension, family history of stroke, irregular pulse, diabetes mellitus, history of heavy smoking, history of alcohol abuse and folate quartile were considered as potential predictive variables for having a history of stroke. Age (years), gender (male, female), residence (community, institutional), presence of dementia, severity of dementia (mild, moderate, severe), folate quartile and body mass index (kg/m²) were included as potential predictors for mortality.

Results

Demographics

Of the participants in this study, 596 (50.9%) were institutional residents and 718 (61.3%) were female. The average age was 81.6 years (range 65–104 years). The 3MS scores for these subjects ranged from 0 to 100 (mean 55.2 ± 26.2); 55.3% were demented. In the demented groups, 249 had a diagnosis of probable Alzheimer’s disease, 183 possible Alzheimer’s disease, 112 vascular dementia, 38 other dementias and 66 had unclassified dementias. Dementia severity ranged from mild (n = 132), through moderate (280) to severe (229).

Folate levels

Overall, 328 subjects (28.0%) were in Q1 while 265 subjects (22.6%) were allocated to Q4. Q1 subjects were more likely to be demented, institutionalized, depressed, have weight loss, have a lower body mass index, have lower serum albumin concentrations and complain of poorer self-rated health (Table 1 and Figure 1). Compared with Q4, Q1 subjects were more likely to be heavy drinkers (21.4% versus 7.7%; P < 0.0001), smokers (39.0% versus 26.2%; P < 0.0013), taking anticonvulsants (7.9% versus 4.2%; P = 0.06)
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and to have feeding problems (27.8% versus 16.2%; \( P = 0.0008 \)).

Folate and cognition

Q1 values were least common in subjects with no cognitive loss (15.5% of these subjects) and increased to 28.0% in CIND and to 32.7% in those with dementia (logistic regression, \( P < 0.05 \)). In CIND, 3MS scores were significantly lower in Q1 as compared with Q4 subjects (62.9 versus 70.4; \( P = 0.003 \)) but there was no significant difference between Q1 and Q4 subjects in the other categories. Neuropsychological testing showed that short-term memory problems were more frequent in Q1 CIND subjects as compared with Q4 (94.7% versus 75.7%; \( P = 0.004 \)). Q1 subjects were more likely to have any type of dementia (Table 2). Between the specific types of dementia, the proportion of Q1 subjects was not significantly different (\( P = 0.34 \)). Vascular cognitive impairment was more common in Q1 subjects as compared with those in Q4 (22.9% versus 18.5%, \( P = 0.19 \)).

Vascular morbidity

Twenty-three percent of Q1 subjects had a history of stroke compared with 17.6% in Q4 (\( P = 0.07 \); relative risk = 1.41, 95% confidence interval = 0.93, 2.1). The frequencies of stroke for Q2 and Q3 subjects were 18.4 and 19.0%, respectively. Five percent of those in Q1 had a history of intermittent claudication compared with 4.1% in Q4 (\( P = 0.059 \); relative risk = 1.22, 95% confidence interval = 0.55, 2.84). We found that 12.5% of Q1 subjects were taking nitrates (a marker for ischaemic heart disease) compared with 9.8% of those in Q4 (\( P = 0.46 \)). Mean Hachinski scores were non-significantly higher in Q1 participants than in Q4 participants (3.7 versus 3.1, \( P = 0.12 \)). The frequency of stroke, dementia, depression and institutionalization was highest in Q1 (Table 2).

Stepwise logistic regression showed that hypertension \((b_1 = 1.02, P < 0.0001)\), low folate quartile \((b_2 = -0.22, P = 0.007)\), male gender \((b_3 = -0.39, P = 0.05)\) and irregular pulse \((b_4 = 0.43, P = 0.046)\) were the only factors significantly associated with an increased likelihood of a history of stroke.

Mortality

Mortality at 2-year follow-up was 31% in Q1 compared with 23.5% in Q2, 25.9% in Q3 and 25.0% in Q4 (\( P = 0.17 \)). At the time of follow-up, Q1 subjects were less likely to rate their health as being the same or better when compared with Q4 subjects (51.1% versus 67.5%, \( P = 0.02 \)).

In the stepwise logistic regression, institutionalization \((b_1 = 0.87, P < 0.0001)\), older age \((b_2 = 0.05, P < 0.0001)\), greater dementia severity \((b_3 = 0.29, P = 0.0001)\) and male gender \((b_4 = -0.64, P = 0.0002)\) were significantly associated with an increased likelihood of death.

Discussion

Hyperhomocysteinaemia is an independent risk factor for vascular disease and is largely attributable to low serum folate levels [3, 6, 12]. Reports of metabolic dysfunction with even 'normal' serum folate levels [1, 2, 31], the declining efficiency of homocysteine metabolism associated with ageing [32] and the high prevalence of hyperhomocysteinemia [2] highlight the potential importance of folate nutrition. In this large study of elderly Canadians, there were non-significant correlations between low folate and a history of stroke and a history of intermittent claudication. Logistic regression showed that being in Q1 was a significant explanatory variable for evidence of stroke, even when the presence of other risk factors was considered.

Many Q1 individuals were demented, all types of dementia being common. There was also a significant relationship between folate levels and depression. Low plasma folate levels have been associated with both dementia [33] and mood disorders [5, 34]. It is possible that low folate could lead to these problems. Impairment in methylation in the central nervous system is thought to occur with low serum folate and methylation deficiencies have been proposed as a pathogenic

| Table 2. Proportions of subjects in the lowest (Q1) and highest (Q4) quartiles with dementia |
|--------------------------------------------------|-----------------|-----------------|---|
| % of subjects, by quartile                        | Q1 \((n = 328)\) | Q4 \((n = 265)\) | \(P\) |
| Dementia (any type)                               | 64.6            | 45.7            | <0.0001 |
| AD (probable and possible)                        | 41.5            | 31.3            | 0.01   |
| Probable AD \((n = 249)\)                         | 23.2            | 18.5            | 0.26   |
| Vascular dementia \((n = 112)\)                  | 11.6            | 8.3             | 0.18   |
| Other types of dementia \((n = 38)\)             | 4.3             | 1.5             | 0.05   |
| Unclassified dementias \((n = 66)\)              | 7.3             | 4.5             | 0.22   |

AD, Alzheimer's disease.
mechanism in neuropsychiatric disease [35]. S-methyl tetrahydrofolate is the primary circulatory form of folic acid and is necessary for the remethylation of homocysteine to methionine. Methionine is the precursor of S-adenosylmethionine, the primary donor for the methylation of neurotransmitters and DNA [35–37]. Significantly lower levels of S-adenosylmethionine, involved in choline synthesis, have been found in the cerebro-spinal fluid of patients with Alzheimer’s disease [38]. S-adenosylmethionine also has antidepressant properties [38].

The similar proportions of subjects in Q1 with different types of dementia suggest that any detrimental effect of low serum folate levels is not restricted to a particular type of dementia. Cognitively intact elderly people with better folate status performed better on the abstraction portion of a neuropsychological battery [39]. In contrast to previous work [40], we found that CIND subjects in Q1 performed significantly worse on the 3MS and were more frequently assessed by a neuropsychologist as having short-term memory difficulties. Better folate status has been found by other investigators to be associated with better Mini-Mental State test scores, function and results on a depression scale [41–43].

Our data could reflect the reduced ability of cognitively impaired individuals to attend to their nutritional needs. Abnormalities in other nutritional indices support this. Q1 subjects were more likely to have problems with feeding. Low serum folate levels in institutional residents have been attributed to increased age, frailty and dementia [44]. Poor nutrition is commonly associated with all of these conditions [45, 46]. Our data confirmed previously reported associations between low folate and alcohol use [28], smoking [27, 29] and taking an anticonvulsant [30].

There were several limitations in our data. Serum homocysteine concentrations were not measured. No central laboratory was used. Red blood cell folate is a better measure of tissue levels than serum folate, which is more sensitive to abrupt changes in intake [47]. As subjects were clinically stable when seen and, because other studies have found a correlation between serum folate and homocysteine concentrations, we do not believe this would negate our findings. Individuals were invited to have clinical examinations without longitudinal data.

Proper folate nutrition has potentially important implications for elderly people. Metabolic folate deficiencies are easily, inexpensively and rapidly correctable and may reduce morbidity and mortality.

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Key points

- Low folate status is associated with the presence of stroke.
- Low serum folate levels are common in all types of dementia.
- Low serum folate level is also associated with a history of weight loss, lower body mass index and lower serum albumin concentrations.
- This may reflect inadequate nutrition in cognitively impaired subjects.

References

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