NeuroReport 10, 2377–2381 (1999)

Evidence for association of anaemia with vascular dementia

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THE present investigation aimed to examine associations of anaemia with dementia. Analysis of community-dwelling, elderly subjects characterized for different dementias failed to confirm a previously reported association of anaemia with Alzheimer's disease (AD) but revealed instead a significant association with vascular dementia (VAD). Nearly 45% of VAD subjects were anaemic, compared with 17% of controls. Close to one-third of all subjects with haemoglobin levels >0.5 g/dl below reference anaemia levels had VAD. Co-existing VAD may explain previous links between AD and anaemia. The association was independent of age, dementia severity and a range of other factors including vitamin B 12 and folate levels. Anaemia can exacerbate focal cerebral ischaemia and could precipitate or amplify VAD symptoms in elderly subjects with vasculopathy. *NeuroReport* 10:2377–2381 © 1999 Lippincott Williams & Wilkins.

Key words: Ageing; Alzheimer's disease; Anaemia; Folate; Haemoglobin; Vascular dementia; Vitamin B12

Introduction

As many as 10–20% of community-dwelling elderly are anaemic [1–3]. In a 1990 case-control study based on informant reports, we noted a trend towards association of Alzheimer's disease (AD) with prior anaemia, although it was not statistically significant (matched pairs odds ratio OR 1.46, 95% confidence interval (CI) 0.73–2.95) [4]. However, a Mayo Clinic case control study based on medical record documentation has now shown a significant association between AD and anaemia prevalent in the year of estimated AD onset or preceding year (OR 1.88; 95% CI 1.17–3.03), although concomitant retrospective cohort analysis of subjects with incident anaemia failed to find an increased risk of AD [1].

These studies did not assess the specificity of anaemia association with respect to other dementias such as vascular dementia (VAD), which often coexist with AD. In addition, use of hospital-presenting subjects introduces biases. The risk of anaemia increases with hospitalization [5,6], and other potentially confounding conditions are more likely to be present. In the retrospective cohort study above [1], anaemia was first detected on or after hospital admission for unrelated conditions in ~70% of subjects. Over one-third were anaemic from surgery and differed in several features, including age, from other anaemic subjects [5]. Anaemias resulting from neoplastic disease, acute infections or internal bleeding due to some closed fractures are also likely to be more common in hospitalized subjects [5].

Community studies are important to avoid such potential biases and clarify the relevance of anaemia to dementia in the general elderly population. A community-based study of approximately 650 elderly Australian subjects initiated in 1991 has measured various factors relating to health and disease in aging [7,8]. We examined retrospectively the association of coincident anaemia with different dementias in these elderly, community-dwelling subjects.

Subjects and Methods

The population from which subjects were drawn has been described in detail elsewhere [7,8]. Briefly, it comprised community-dwelling, non-institutionalized people living in the Central Sydney area (mean age at the time of haemoglobin measurement 84.9 ± 3.7 years; men 84.2 ± 3.2 years, women 85.5 ± 4.0 years). All studies have full institutional ethics approval with written, informed consent obtained for all participants. Subjects were eligible if they were community dwelling and spoke English well enough to be interviewed without an interpreter. Although selection was otherwise random and independent of ethnic background, essentially all subjects were Caucasian. Haemoglobin levels were measured by accredited techniques within 14 ± 5 months after medical assessment, for 316 surviving subjects (167 men and 149 women) con-

senting to both medical and blood assessment. Probable AD and VAD were diagnosed with NINCDS-ADRDA and DSM-IV criteria, which incorporate criteria for attributing dementia to co-existing AD and VAD. Other dementias (e.g. dementia with Lewy bodies, alcoholic dementia, frontal lobe syndrome) and disorders were diagnosed on clinical grounds [7,8]. Statistical analyses with haemoglobin as a dichotomized variable (see below) used one-tailed exact Pearson χ^2 tests when three or more categories were analysed and Fisher's exact tests for 2×2 tables.

Results

Initially we used World Health Organization (WHO) criteria for anaemia, namely haemoglobin levels < 13 g/dl for men and < 12 g/dl for women [9]. Disease onset data and haemoglobin data prior to disease diagnosis were not available but in cross-sectional analysis ~25% of all subjects with an AD diagnosis were anaemic by WHO criteria, the same proportion as in the Minnesotan AD group [1]. Consequently, although the proportion of anaemic non-demented controls was slightly higher (17% compared with 13%), our data could be interpreted as suggesting a weak association of anaemia with AD if VAD were not taken into account. However as 40% of the anaemic AD subjects in our sample were diagnosed with co-existing VAD (Table 1), we tested separately for association with anaemia in the subset diagnosed only with AD and no other dementias (pure AD) and the subset with co-existing VAD (AD + VAD). We also examined the group diagnosed only with VAD and no other dementias (pure VAD) and the group diagnosed with other dementias (Table 1).

Anaemia correlated with diagnosis of co-existing AD and VAD ($p = 0.012$) but not with pure AD ($p = 0.401$). Over 50% of all subjects with both VAD and AD were anaemic, compared with 20% of both pure AD and non-demented controls. This suggests reported associations of AD with anaemia might depend on co-existing VAD in many AD subjects, a possibility not addressed previously [1]. Irrespective of gender, ~35% of subjects diagnosed with pure VAD were anaemic, double the proportions of anaemic non-demented subjects (or anaemic AD subjects), but this failed to reach significance at the 0.05 level ($p > 0.087$). However, as discussed later, clinical distinction of pure VAD from AD + VAD combined is not definitive. When we exam-

Table 1. Anaemia is associated with VAD but not AD

	n	% Anaemic (*n*)	Pearson χ^2	Significance[a]
All subjects				
Non-demented	245	17.1 (42)		
Pure AD	40	20.0 (8)	0.194	0.401
Pure VAD	14	35.7 (5)	3.075	0.087
AD + VAD	9	55.6 (5)	8.494	0.012
Other	8	0 (0)		
Overall[b]			12.814	0.007
All VAD[c]	23	43.5 (10)	9.325	0.005
Men				
Non-demented	119	19.3 (23)		
Pure AD	15	13.3 (2)	0.315	0.440
Pure VAD	8	37.5 (3)	1.520	0.208
AD + VAD	1	0 (0)	0.239	0.808
Other	6	0 (0)		
Overall[b]			3.770	0.225
All VAD[c]	9	33.3 (3)	1.014	0.266
Women				
Non-demented	126	15.1 (19)		
Pure AD	25	24.0 (6)	1.202	0.207
Pure VAD	6	33.3 (2)	1.426	0.243
AD + VAD	8	62.5 (5)	11.505	0.005
Other	2	0 (0)		
Overall[b]			12.687	0.009
All VAD[c]	14	50.0 (7)	10.160	0.005

The proportions of anaemic subjects by WHO criteria (with the number in parentheses) is given for groups 1, non-demented; 2, pure AD (without VAD or other neurological disorders); 3, pure AD (without AD or other neurological disorders); 4, AD with co-existing VAD and 5, all other neurological disorders. [a]Significance relative to non-demented subjects was examined by Fisher's exact test (one-tailed, 2×2 table).
[b]Overall *p* values were calculated by exact Pearson χ^2 tests (one-tailed, 5×2 table).
[c]All subjects with VAD (groups 3 and 4) were then combined to give the 'all VAD' group and compared with non-demented subjects by Fisher's exact 2×2 test (one-tailed).

ined all subjects with a VAD diagnosis (pure VAD and AD + VAD combined), the association with anaemia previously observed for the AD + VAD group was strengthened ($p = 0.005$), consistent with a specific association of VAD and anaemia, rather than weakened, as would be predicted if anaemia were associated solely with the combination of VAD and AD and not with VAD alone. Nearly 45% of all VAD subjects were anaemic, compared with ~17% of non-demented subjects. Association with anaemia occurred primarily in women ($p = 0.005$), with 50% of all women diagnosed with VAD being anaemic. There was no significant association in men however numbers were small. Only nine men in total were diagnosed with VAD and of these, three were anaemic.

Clinical distinction of VAD from AD by NINCDS-ADRDA and DSM-IV criteria is not definitive without neuropathological evaluation but can be strengthened by evidence such as ischemic scores derived by various systems and certain focal neurological symptoms and signs (reviewed in [10]). All subjects with anaemia and diagnosed VAD each had at least 3 (and most at least 5), of the following corroborative features: revised ischemic scores > 6 [11] ($n = 9$), hypertension ($n = 8$), gait ataxia ($n = 10$, of whom seven also had gait slowing), urinary incontinence ($n = 5$) or one or more other relevant symptoms or signs (all $n = 1$, hemiplegia, marche á petit pas, falls, reduced density on brain CT, parietal cerebrovascular atrophy with visual field defect, delirium or confusion, transient ischemic attack, atrial fibrillation, peripheral vascular disease).

The mean age (± s.e.) of subjects with VAD and anaemia was 85.3 ± 1.5 years (range 80–95 years). The elderly in general have a higher prevalence of anaemia and marginal anaemia is sometimes considered a normal response to ageing [12–14]. However the correlation of VAD and anaemia persisted when age was added to a logistic regression model predicting anaemia from all VAD, so it is not solely an indirect association arising with age (stepwise regression coefficient for age r = 0.000+, $p = 0.359$). Nonetheless, other spurious effects might arise due to widespread marginal anaemia. To examine this, we re-stratified haemoglobin data, defining well/mildly anemic as > 12.5 g/dl in men and > 11.4g/dl in women. These figures, ~0.5 g/dl below the WHO anaemia criterion, were chosen as being closest to the 50th percentile for the WHO anaemic groups of each sex. Of subjects anaemic by WHO criteria, 11 of 28 men (39%) and 17 of 32 women (53%) fell below these levels and were classed as more anaemic, representing 7.4% of men and 10.2% of women overall (the lowest levels were 9.3 and 7.7 g/dl in men and women, respectively).

More pronounced anaemia was again associated with VAD (overall Pearson χ^2 20.353, $p = 0.000+$, Table 2). More anaemic subjects were over five times likelier to have VAD than those with marginal or no anaemia. Approximately 80% of women and 70% of men with VAD who were anaemic by WHO criteria were classed as more anaemic. The proportion of women with VAD who were more anaemic was nearly seven times the proportion of non-demented women. The proportion of men with VAD who were more anaemic was over three times corresponding proportions of non-demented or AD males, but numbers were small and this was not significant (Table 2).

To determine whether VAD and AD subjects differed in dementia degree, dementia severity as gauged by Mini-Mental State Examination (MMSE) scores was examined across the full group of clinically assessed subjects. There was no significant difference by ANOVA ($F = 1.143$, $p = 0.323$) in MMSE between subjects with AD ($n = 62$), VAD ($n = 19$) or both AD and VAD ($n = 16$). There was also no significant difference in MMSE by ANOVA of the six groups formed by incorporating anaemia, by the more stringent criteria ($F = 0.980$, $p = 0.438$).

Indirect association between anaemia and VAD could arise for many reasons, including chronic disease, malnutrition and medication use. Around 200 different medical conditions were reported over the full population [7,8], with use of ~40 different

Table 2. Association of more marked anaemia with VAD but not AD

	All subjects		Men		Women	
	n	% More anaemic	*n*	% More anaemic	*n*	% More anaemic
Non-demented	245	6.5 (16)	119	6.7 (9)	126	6.3 (8)
AD alone	40	10.0 (4)	15	6.7 (1)	25	12.0 (3)
All VAD	23	34.8 (8)	9	22.2 (2)	14	42.9 (6)
χ^2		20.353		2.856		18.264
Overall *p*		0.000+		0.111		0.000+

Haemoglobin levels were characterized as well/mildly anaemic or more anaemic, as described in Results. Proportions of more anaemic subjects are shown, with numbers of anaemic subjects in parentheses. Significance (one-tailed) relative to non-demented subjects was assessed by Fisher's exact (2 × 2) test with exact Pearson χ^2 tests to calculate overall *p* values across the groups.

medication classes. Abnormal haematological and biochemical measures were common (Creasey *et al*., in preparation). While unrealistic to propose all factors can be examined in a single study, preliminary analysis shows no evidence ($p > 0.05$) for significant contributions of chronic diseases (including renal failure gauged clinically or by creatinine status) or medications (notably nonsteroidal anti-inflammatory drugs, aspirin or warfarin, vitamin B 12 and folate).

Discussion

The high prevalence of anaemia in older populations has been recognized for decades. Our analysis, like others [1–3], suggests it has not abated in recent years. The possibility of an association with dementia of any kind is, therefore, of considerable interest. Our data suggest anaemia is associated with VAD rather than AD and that co-existing VAD could underlie apparent associations with AD [1]. The reported association with AD and the present association with VAD occurred primarily in women; however, gender linkage remains to be confirmed as men in both studies did show trends towards associations of anaemia with dementia and numbers were small. Differential attrition of men with vascular risk factors could result in fewer men in the groups of interest.

Without neuropathological examination, dementia is likely to be misclassified in some individuals. While unqualified validation of the association must await studies on neuropathologically confirmed cases, this may be less of a problem here than is sometimes the case. Clinical classification is likely to be most prone to error in discriminating combined AD and VAD from pure VAD (reviewed in [10]); however, this error source is non-existent when an all VAD group is used, as was done here. Furthermore, all anaemic subjects diagnosed by NINCDS-ADRDA and DSM-IV criteria as having VAD (with or without AD) displayed a range of additional features substantiating the classification.

The retrospective data available to us were cross-sectional (haemoglobin measurements prior to dementia onset were not available) and do not address whether anaemia contributes causally to VAD. An earlier study of AD development in an anaemic cohort [1] failed to show causation but did not assess VAD development and included a substantial proportion of post-operative anaemia, likely to differ in many features from anaemias of senescence in general [5]. A high proportion of more anaemic subjects may also be needed to reveal effects in such studies.

While neither age nor dementia severity (as gauged by MMSE) appeared to be important factors, an indirect association of anaemia with VAD could arise from a variety of other common underlying causes, including chronic diseases such as inflammatory conditions or renal failure, malnutrition and some medications. Of these, renal failure is perhaps most obviously consistent with a specific association with VAD rather than AD. While diagnosed chronic renal failure did not account for the association, undiagnosed renal failure may be relatively common in the elderly [1]. We are continuing to examine factors that may contribute to indirect effects but comprehensive investigations are beyond our present scope: anaemias of senescence themselves remain poorly understood despite numerous studies. The Minnesotan study [1] associating anaemia with AD also examined various factors that might contribute indirectly to the relationship and failed to find any effects, with the exception of age (which was not significant in our analysis).

The association could also arise directly. The absence of any biologically plausible mechanism may be the greatest barrier to considering a direct causal relationship between anaemia and AD [1]. This is not the case for anaemia and VAD. In healthy individuals, brain oxygenation is maintained under most conditions by regulation of cerebral blood flow and other factors. However, such compensatory mechanisms may not fully protect against the effects of anaemia on brain oxygen supply even without the added burden of impaired flow regulation due to vasculopathy [15,16]. Anaemia combined with widespread or localized cerebrovasculopathy could substantially increase risks of chronic global or focal ischaemia. Evidence for a direct association is also provided by work showing anaemia can contribute to neurological injury from focal ischaemic insults by limiting penumbral oxygen uptake [16]. Both scenarios are biologically plausible mechanisms whereby anaemia could combine with vasculopathy to cause or precipitate VAD. Moreover in either scenario, anaemia could worsen cognitive consequences of co-existing cerebrovasculopathy irrespective of whether or not the initial causative associations are direct.

Presenting features of anaemia in the elderly may overlap many of the features that can accompany dementia, including irritability, apathy, forgetfulness, acute confusional states, delusions, hallucinations, postural hypotension, dizziness with falls, increase in postural sway, loss of balance and visual disturbances. While some of these may arise because the demented in general may be more prone to malnutritional anaemias, treating the anaemia could ameliorate some of these problems, similar to the cognitive benefits achieved by treating anaemia in

chronic renal failure [15]. Treatment might not only benefit VAD subjects by slowing progression or lessening cognitive deficits but might also delay symptom onset in at-risk nondemented elderly. In any event, the substantial proportion of anaemic VAD subjects may need consideration in studies where anaemia could influence individual responses or outcome assessment.

Conclusion

Overall, our data suggest anaemia in community-dwelling elderly is associated with VAD rather than AD and suggest that co-existing VAD could underlie previously reported associations with AD. More anaemic subjects were more likely to have VAD and this was independent of age or dementia severity gauged by MMSE. We hope these findings stimulate larger community-based investigations of the associations between anaemia and dementia.

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ACKNOWLEDGEMENTS: This work was supported by the National Health and Medical Research Council of Australia, the Australian Public Health Research and Development Committee (PHRDC), the Sir Zelman Cowen Universities Fund, Alzheimer's Association Australia and the Ageing and Alzheimer's Research Foundation. We also thank Dr J.J. Kril and B.L. Kyngdon for their assistance.

Received 28 April 1999; accepted 3 June 1999