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Neurobiology of Aging 27 (2006) 278–284

NEUROBIOLOGY OF AGING

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Anaemia increases the risk of dementia in cognitively intact elderly

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Received 29 July 2004; received in revised form 6 January 2005; accepted 1 February 2005

Abstract

Although cross-sectional studies found an association between anaemia and dementia, longitudinal studies provided contradictory results. We hypothesize that anaemia might increase the risk of developing dementia because of chronic brain hypo-oxygenation.

Using baseline data from a community-based longitudinal study, the Kungsholmen Project, Stockholm, Sweden, we clinically followed 1435 non demented subjects aged 75–95 years for 3 years to detect incident dementia cases (DSM-III-R criteria).

Subjects that fulfilled WHO criteria for anaemia, baseline haemoglobin concentration; 130 g/L (men) and 120 g/L (women), had a higher hazard ratios (HR) of developing dementia 3 years later (HR 1.6, 95% CI: 1.1–2.4). In persons with good baseline cognition (MMSE $\geq$ 26, $n = 1139$), the association was stronger and still significant after adjustments for conditions potentially related to anaemia and dementia, such as chronic diseases, inflammatory markers, and indicators of nutritional status. The HR was increased even when different haemoglobin cut offs for anaemia definition were used. Thus, anaemia is suggested to be a new potential modifiable risk factor for dementia.

Keywords: Haemoglobin concentration; Anaemia; Dementia; Alzheimer disease; Aging; Epidemiology

1. Introduction

Anaemia is very common after age 65 years, accounting for 4.2% [22] to 28% [14] when WHO criteria [35] are applied in different gender and age groups. In addition, anaemia incidence has been reported to increase with age [2]. Dementia and Alzheimer disease (AD) are also frequent occurrences in the elderly, and both prevalence [20] and incidence [12] increase exponentially with age. Although a complete blood count is recommended [27] to identify "potentially reversible cognitive impairment" [7], apart from pernicious anaemia which is a well-known cause of "reversible dementia" [26], the role of anaemia on cognition, independent of Vitamin B12 levels, is controversial. A study based on informants' reports, found a higher, although not statistically significant, risk of Alzheimer disease (AD) in subjects with a history of anaemia [6]; a case–control study from the Mayo Clinic [5] showed that anaemia in the year prior to dementia diagnosis, was related to incident AD but the association was not confirmed prospectively. Finally, an association between anaemia and vascular dementia has been reported by a cross-sectional study in Australia, but no association was found with AD [21].

The current study used data from the Kungsholmen Project, a longitudinal population-based study carried out in Stockholm, Sweden, to evaluate the role of anaemia on the development of dementia. Since cerebral hypo perfusion has been suggested to be involved in neurodegeneration [32], and an abrupt reduction in brain oxygenation is associated with lower cognitive performance [8], we hypothesized that a chronic anaemic status might increase the risk of developing dementia. To exclude the effect of other possible confounders, we tested this hypothesis in three models where

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doi:10.1016/j.neurobiolaging.2005.02.007

the effect of different covariates was taken into account separately. The first model included chronic diseases, as some of them have been related to development of dementia, and they might also lower haemoglobin concentration. The second model took into account markers of inflammation, as this has been related to dementia [28] and low haemoglobin concentration might be due to an inflammatory state ("anaemia of inflammation") [23]. The third model included nutritional indicators, due to the fact that weight loss has been associated with development of dementia [34], and malnutrition, which is frequent in the elderly, might lead to low haemoglobin concentration. Finally, all the previous variables were considered together in a fully adjusted model.

2. Methods

2.1. Study population

We used data from baseline and 3-year follow-up examination of the Kungsholmen Project, a longitudinal, population-based study on aging and dementia. Details of the study design have been already reported [11]. Briefly, all inhabitants living in Kungsholmen area (Stockholm, Sweden) aged 75 years and above in October 1987 (baseline) were asked to take part in the project. Of the 2368 eligible subjects, 1810 (76.4%) participated in the screening phase, which included an interview by trained nurses, assessment of cognitive functioning using Folstein's Mini-Mental State Examination (MMSE) [10], and collection of routine blood samples.

Prevalent dementia cases at baseline were identified with a two-phase study design according to DSM-III-R criteria [1]. There were 1475 non demented persons at baseline, and we excluded subjects that scored lower than 20 on MMSE ($n = 31$, 1.7%), and persons with age over 95 years or unknown educational background ($n = 9$, 0.5%). Baseline haemoglobin concentrations were available for 1377 (96%) subjects.

2.2. Ethical issues

The aim and the study design of the project were explained to all subjects. Confidentiality of collected information was assured, and consent was obtained from all participants. The project was approved by Karolinska Institutet Ethics Committee.

2.3. Baseline variables

2.3.1. Haemoglobin concentration and anaemia definition

Haemoglobin concentration was measured at baseline by standard techniques. Missing data ($n = 58$) were due to persons refusing to give blood samples or to technical problems (haemolysis). First, we defined anaemia using WHO criteria [35] (haemoglobin concentration; 130 g/L for men and 120 g/L for women). However, as these criteria may be too restrictive when applied to an elderly population [3], we chose also cut offs based on the percentiles of haemoglobin concentration in the study population. The lowest 25th and 5th percentiles of the sex-specific haemoglobin concentration distribution provided two further definitions of anaemia. The cut offs for the lowest 25th percentile were 135 g/L for men and 129 g/L for women, and for the lowest 5th percentile 117 g/L for men and 116 g/L for women, respectively.

2.3.2. Socio-demographics and anthropometrics measures

Data on sex, age, and number of years of education were collected during the structured interview. In this study, education was dichotomised into high (8 years or more) or low (7 years or less), based on a previous report [24]. Nurses measured weight and height, and the body mass index (BMI) was calculated as (weight (kg)/(height (m^2))), with low BMI defined as being the lowest 25th percentile (≤ 21.4 kg/m^2). Information on weight or height was missing for 172 (12.5%) subjects.

2.3.3. Laboratory parameters

At baseline, albumin, white blood cell count, and blood sedimentation rate were measured by standard techniques from venous blood samples, and data were missing for 99, 58, and 68 subjects, respectively. Low albumin was defined as albumin concentration in the lowest 25th percentile (<41 g/L). The values chosen as cut off points for high white blood cell count ($\geq 7.9 \times 10^9$/L) and high blood sedimentation rate (≥ 20 mm/h for men and ≥ 15 mm/h for women) were defined according to recommended laboratory values [17].

2.3.4. History of chronic disease

History of disease was collected from the Stockholm Inpatient Register System, a computerized data-set that includes discharge diagnoses from all hospitals in Stockholm from 1969 onwards. Main and additional diagnoses for each hospital admission were coded according to the International Classification of Diseases, eighth and ninth revisions (ICD-8 and ICD-9). From 1969 until the baseline examination date, 1378 (96.0%) subjects were admitted to hospital at least once. History of chronic diseases between 1969 and the baseline examination included the following diagnoses:

hypertension (ICD-8: 400–404, ICD-9: 401–405);
diabetes (ICD-8: 250, ICD-9: 250);
cerebrovascular disease (ICD-8: 430–438, ICD-9: 430–438);
congestive heart failure (ICD-8: 427–428, ICD-9: 427–428);
coronary heart disease (ICD-8: 412–413, ICD-9: 410–414);
chronic obstructive pulmonary disease (ICD-8: 491–493, ICD-9: 491–493);
hypothyroidism (ICD-8: 243–244, ICD-9: 243–244);
chronic renal failure (ICD-8: 582–584, ICD-9: 585–586).

2.4. Diagnosis of dementia

The same protocol was used both at baseline and at the 3-year follow-up examination to detect prevalent and incident dementia cases, respectively. Clinically definite dementia was diagnosed according to DSM-III-R criteria [1]. First, a preliminary diagnosis was made by the physician that performed the clinical examination, which was then reviewed by a specialist blinded to the previous judgement. In case of disagreement, another specialist was consulted and a final agreement was reached. To verify the presence of dementia in subjects that died during the follow-up period ($n = 291$), medical records and death certificates were collected and reviewed by the specialists, and diagnoses were made using the same procedure as above. For a diagnosis of dementia of Alzheimer type, all other specific causes of dementia had to be excluded and a gradual onset with progressive deterioration was required. Vascular dementia (VaD) diagnosis was based on clinical features of dementia, including abrupt onset, stepwise deterioration, temporally related stroke history, and focal neurological deficits.

2.5. Statistical analyses

All analysis were conducted using SPSS Version 10.0.

Chi-square and Student's *t*-tests were used to compare proportion and mean differences in persons with or without anaemia according to different haemoglobin cut offs. Cox proportional hazard models were used to estimate the hazard ratios (HR) and the corresponding 95% confidence intervals (CI) of developing dementia over 3 years in subjects with low levels of haemoglobin at baseline compared to persons with normal levels. Onset of dementia was assumed as being halfway between baseline examination and date of follow-up examination or death. Subjects that died without a diagnosis of dementia were censored at day of death, and subjects still alive and not demented were censored at the day of follow-up examination. First, the analysis was carried out using WHO criteria for anaemia, adjusting for demographic features and cognitive status at baseline. The introduction of MMSE strongly modified the association. Stratified analysis by MMSE showed that the association persisted only among subjects with intact cognition (MMSE score ≥ 26). In order to be conservative about the cognitive status and exclude subjects in the preclinical phase of dementia, further analyses were carried out only in cognitively intact subjects (MMSE ≥ 26, $n = 1139$). In order to verify whether other concurrent conditions could bias the association, we assessed the relationship within three different models, all of which included also sex, age, and education. The chronic disease model made further adjustments for hypertension, diabetes, cerebrovascular disease, heart failure, coronary heart disease, chronic obstructive pulmonary disease, hypothyroidism, and chronic renal failure. The inflammation model adjusted for markers of acute phase reaction available in the database such as white blood cell count and blood sedimentation rate. The nutrition model adjusted for indicators of the nutritional status, such as albumin plasmatic concentration and BMI. Finally, a full adjusted model was carried out by entering all the previous variables.

3. Results

Table 1 shows the main features of the study population according to different haemoglobin concentration cut offs: lower haemoglobin concentration was associated with older age ($p < 0.01$) and lower score on baseline MMSE ($p < 0.05$).

According to WHO criteria, the prevalence of anaemia in the dementia free cohort of the Kungsholmen Project was 15.7% ($n = 54$) in men and 7.3% ($n = 75$) in women ($p < 0.01$) (Fig. 1).

The follow-up examination took place approximately 3 years after baseline (mean follow-up period 3.4 ± 0.5 years). At 3-year follow-up, mortality rate was significantly higher among subjects with anaemia ($n = 43$, 37.1%) compared to

Table 1
Baseline characteristics of the dementia free cohort according to different anaemia definitions

	25th percentile[a]		WHO criteria[b]		5th percentile[c]	
	Above	Below	Above	Below	Above	Below
Gender						
Female sex (*n*, %)	775 (75.0)	258 (75.2)	958 (76.8)	75 (58.1)[§]	982 (25.0)	51 (25.0)
Male sex (*n*, %)	259 (25.0)	85 (24.8)	290 (23.2)	54 (41.9)	327 (75.0)	17 (75.0)
Education						
Low (*n*, %)	590 (57.1)	221 (64.4)[§]	724 (58.0)	87 (67.4)[§]	769 (58.7)	42 (61.8)
High (*n*, %)	444 (42.9)	122 (35.6)	524 (42.0)	42 (32.6)	540 (41.3)	26 (38.2)
Age (years) (mean ± S.D.)	80.9 ± 4.6	82.3 ± 5.1[#]	81.1 ± 4.7	82.4 ± 5.3[#]	81.1 ± 4.7	82.9 ± 5.5[#]
MMSE (score) (mean ± S.D.)	27.0 ± 1.9	26.7 ± 1.8[#]	26.9 ± 1.9	26.6 ± 1.9[#]	26.9 ± 1.9	26.5 ± 2.2

[a] Haemoglobin cut off: women 129 g/L and men 135 g/L.
[b] Haemoglobin cut off: women 120 g/L and men 130 g/L.
[c] Haemoglobin cut off: women 116 g/L and men 117 g/L.
[§] Significant difference between subjects above and below the haemoglobin cut off, χ^2 $p < 0.05$.
[#] Significant difference between subjects above and below the haemoglobin cut off, independent simple *t*-test $p < 0.05$.

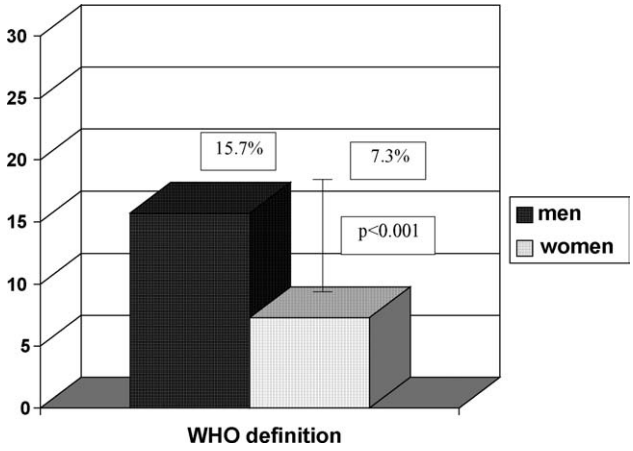

Fig. 1. Anaemia prevalence according to WHO criteria.

persons without ($n = 227$, 20.7%) ($p < 0.001$). The global incidence rate of dementia was 5.2/100 person-year. One hundred and eighty-nine (19.4%) participants received a dementia diagnosis at follow-up examination, while only 18 (6.2%) of subjects that died during the follow-up period received a diagnosis through medical records and death certificates.

Table 2 shows the HR of developing dementia in anaemic subjects (WHO criteria), compared to persons without anaemia. Anaemia at baseline was associated with a 60% increased risk of developing dementia after 3 years of follow-up.

Adjustment for sex, age, and education did not affect the association but when the baseline MMSE score was included, the association was no longer significant. For that reason we stratified by two levels of cognitive performance at baseline, *lower* (MMSE < 26, $n = 296$, 21.0%) and *higher* (MMSE ≥ 26, $n = 1139$). Among persons with lower cognition there was no significant association between anaemia and development of dementia. Conversely, among cognitively intact subjects the risk of developing dementia was twice as higher in anaemic than in non anaemic persons. Consequently, all further analyses were conducted in the 1139 persons with good baseline cognitive performance.

The association between anaemia and dementia was further explored by using the other two definitions. Regardless of the cut offs used, anaemia increased the risk of dementia, after adjustment for sex, age, and education. The HR was higher when lower cut offs were considered, suggesting a dose–response effect.

Table 3 shows the HR of dementia for subjects with anaemia after adjustment for different potential confounders. The direction and the strength of the association between anaemia and development of dementia did not change after adjustment for either chronic disease, markers of inflammation, or nutrition indicators. Moreover, when all the variables were simultaneously included in a fully adjusted model, presence of anaemia, defined using WHO criteria or 5th percentile, was still associated with a two-fold higher risk of dementia. A further analysis performed only on subjects that survived until follow-up examination showed similar results (data not shown).

The impact of anaemia on the development of different types of dementia was also evaluated. At 3-year follow-up examination, 146 demented subjects (77.2%) received an AD diagnosis and 24 persons (12.7%) had a VaD diagnosis. Because of the small number of incident cases, dementia due to other causes (10.1%) was not considered in the following

Table 2
Risk of dementia over 3 years of follow-up due to anaemia (WHO criteria)

	Dementia		HR (95% CI)		
	Anaemia, *n* (%)	Non anaemia, *n* (%)			
All subjects	25 (21.6)	170 (15.5)	1.6 (1.1–2.4)[a]	1.5 (1.0–2.3)[b]	1.3 (0.8–2.0)[c]
Subjects with MMSE score <26	9 (30.0)	78 (35.7)	0.8 (0.4–1.7)[a]	0.7 (0.4–1.5)[b]	0.7 (0.4–1.5)[c]
Subjects with MMSE score ≥26	16 (18.6)	92 (10.4)	2.1 (1.2–3.6)[a]	2.2 (1.3–3.8)[b]	2.2 (1.3–3.7)[c]

[a] Unadjusted.
[b] Sex, age, and education adjusted.
[c] Sex, age, education, and MMSE adjusted.

Table 3
Risk of dementia due to anaemia defined by different cut offs in subjects with good cognition

	HR (95% CI)				
	Basic model[a]	Chronic diseases model[b]	Inflammation model[c]	Nutrition model[d]	Full adjusted model[e]
<25th percentile	1.4 (0.9–2.1)	1.4 (0.9–2.2)	1.4 (0.9–2.1)	1.3 (0.8–2.1)	1.2 (0.7–2.0)
WHO criteria	2.2 (1.3–3.7)	2.2 (1.3–3.7)	2.1 (1.2–3.7)	2.2 (1.2–4.2)	2.0 (1.0–3.8)
<5th percentile	3.0 (1.5–5.7)	2.6 (1.3–5.0)	2.6 (1.4–5.1)	2.6 (1.2–5.6)	2.2 (1.0–4.9)

[a] Age, sex, and education.
[b] History of hypertension, diabetes, cerebrovascular disease, heart failure, chronic coronary disease, chronic obstructive pulmonary disease, hypothyroidism, chronic renal failure, age, sex, and education.
[c] High white blood cells, high blood sedimentation rate, age, sex, and education.
[d] Low albumin, low body mass index, age, sex, and education.
[e] All the previous variables together.

analysis. After adjustment for sex, age, and education, anaemic (WHO criteria) subjects had a two-fold higher risk of developing AD (HR, 95% CI: 2.1(1.1–4.2)); the point estimate for VaD was similar but the association did not reach statistical significance (HR, 95% CI: 2.0 (0.4–9.3)).

Two supplementary analyses were performed on a small sample of subjects ($n = 394$) that had a more extensive chemistry panel, in order to explore the influence of two potential confounders. First, in order to exclude whether anemia was due to deficiencies in Vitamin B12 and folic acid [33], we compared the levels of these two vitamins in anaemic and non anaemic subjects and found no difference (mean ± S.D. Vitamin B12 concentration 295.84 ± 298.88 pmol/L versus 329.45 ± 280.39 pmol/L, $p = 0.525$; mean ± S.D. folic acid concentration 26.16 ± 15.63 nmol/L versus 21.93 ± 14.10 nmol/L, $p = 0.513$, respectively, in anaemic subjects and non anaemic). Second, as chronic renal failure has been found to be associated with cognitive impairment [18], we performed an additional Cox proportional hazard model with adjustments for baseline creatinine plasmatic concentration, and the associations between anaemia and risk of subsequent dementia was unchanged (data not shown).

4. Discussion

In our prospective study, anaemic subjects with good baseline cognitive performance had a two-fold higher risk of developing dementia 3 years later than persons without anaemia. The association was still substantial and significant after adjustments for a number of potential confounders such as history of chronic diseases, inflammatory markers, or indicators of malnutrition. The hazard ratios of incident dementia was higher when lower haemoglobin cut offs were used to define anaemia, suggesting a dose–response relationship between haemoglobin levels and risk of dementia. The biological mechanism underlying this association could be a chronic brain hypo-oxygenation due to anaemia, which is plausible considering a number of experimental and epidemiological findings. A critical reduction in brain oxygenation has been shown to cause reversible cognitive impairment [8] and, conversely, an increased availability of circulating blood oxygen improves cognitive performance. A double-blind, placebo-controlled study showed an improvement in cognitive performance after oxygen administration [29]. Epidemiological studies reported that low blood pressure [25] increases the risk of incident dementia, and chronic obstructive pulmonary disease [31] has been associated with lower cognitive performance. These conditions might share a common final pathway with anaemia, all of them leading to hypoxia involved in the neurodegenerative process [4].

In addition, in healthy subjects, a regulator mechanism works to keep the cerebral flow constant even under stressful conditions but, in elderly persons, this compensatory mechanism might be impaired by aging itself or age-related cerebrovascular disease. Our results suggest a role of anaemia on the development of both AD and VaD, and this is consistent with the increasing amount of literature suggesting that different types of dementia share the same risk factors [9,13,19] and that, especially among older subjects, dementia might be due to both neuro-degeneration and vascular pathology [15,16].

The association between anaemia and dementia was persistent only in subjects with good cognition; the lack of association among subjects cognitively impaired might be due to an underestimation of dementia cases among deceased subjects. In other words, person with lower cognition and lower haemoglobin concentration, that had a higher risk of dying during the follow-up, had a lower probability of being classified as demented in our study. Alternatively, the lack of an association among subjects with lower cognition might reflect the fact that anaemia plays a role in the development of dementia only in the earlier phases of the pathogenic process. Thus, this finding supports the hypothesis that anaemia is related to dementia development and not vice versa, as subjects in the pre clinical phases of dementia often show detectable signs of cognitive impairment [30].

To our knowledge, only one study in literature investigated the association between anaemia and development of dementia over time, and our results are partially consistent with it [5]. In a case–control study, they found an almost two-fold higher risk of dementia in anaemic subjects than in subjects with normal haemoglobin concentration, but then they failed to confirm the association over a 5-year period.

In our prospective study, after 3 years of follow-up the HRs of anaemic subjects was still twice as high, and since multiple adjustments did not affect the significance of the association, the relationship between anaemia and development of dementia seems to be independent of other chronic conditions that are potentially related to anaemia and dementia. In addition, we examined actual haemoglobin concentration, which is a more accurate measure than reports concerning history of anaemia or discharge records. Indeed, even a-symptomatic cases of mild anaemia have been included in our study.

As WHO criteria to define anaemia have been criticized in an elderly population [22] we verified the association using different haemoglobin cut offs. A higher HR of incident dementia was present in subjects with lower haemoglobin concentration. These findings support our hypothesis: the lower the haemoglobin concentration and more severe the brain hypo-oxygenation, the more likely is the development of dementia.

Some limitations in our study deserve comments, especially the assessment of confounders. First, as we gathered information about history of diseases through medical records, we could not assess diseases that did not require hospitalisation. Nevertheless, we are quite confident that the most severe diseases affecting both haemoglobin concentration and cognition have been taken into account. If diseases from medical records were underreported, this could have led to an underestimation of the effect of confounders. We tried to minimize the error adjusting for the variables available in the data set, for

example, including in the model laboratory chemistry variables such as creatinine clearance to measure renal function or albumin as nutritional marker but results did not change. Second, BMI and albumin are coarse indicators of malnutrition but they are commonly used in large epidemiological studies to assess the general nutritional status of an elderly population. Third, more precise inflammatory markers were desired but they were not included in the Kungsholmen Project database. Fourth, high plasma homocysteine levels have been related to dementia [36] as well as low levels of Vitamin B12 and folic acid [33] that might also be associated with anaemia and play a confounding role. However, concerning dementia diagnosis we are certain that none of the demented subjects had impaired cognition due to lack of Vitamin B12 and folic acid because of the strictness of the criteria used in the study design and no differences were detectable in Vitamin B12 and folic acid status between anaemic and non anaemic subjects.

In conclusion, this is the first longitudinal population-based study to point out anaemia or low haemoglobin concentration as a possible risk factor for dementia. Our findings might have important clinical and public health implications: first, to better understand the mechanisms involved in neuro-degeration, and second, to recommend investigation and treatment of anaemia in the elderly population even if they are a-symptomatic and still cognitively intact. As haemoglobin concentration is easy to measure and anaemia might be suitable of treatment, further population-based studies or clinical trials are needed to confirm the role of anaemia as a "modifiable" risk factor for dementia.

Acknowledgments

The authors thank all workers of the Kungsholmen Project for data collection and management and the Swedish Research Council. This study was supported by grants (Borsa di studio di Perfezionamento all' Estero) from the University of Ferrara (Italy).

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