Anaemia increases the risk of dementia in cognitively intact elderly

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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 hypoxoxygenation. 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 ≥ 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.

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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...
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 included 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 anthropometric 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 (m2)). 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 (>7.9 × 109/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);
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 analyses 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...
Fig. 1. Anaemia prevalence according to WHO criteria.

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 analyses.
Due to deficiencies in Vitamin B12 and folic acid, 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 pmol/L versus 21.93 ± 14.10 pmol/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 vari-
ables such as creatinine clearance to measure renal failure or
albumin as a nutritional marker but results did not change. Sec-
ond, 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 popu-
lation. Third, more precise inflammatory markers were ad-
sired 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 examined 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-degeneration, and second, to recommend
investigation and treatment of anaemia in the elderly pop-
ulation 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.

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References

Association. 1987 [revised].

LJ. Incidence of anemia in older people: an epidemiologic study in

[3] Baldacci L. Epidemiology of anaemia in the elderly: information on

[4] Barre NG, Palacios-Feliz R, Lukow WJ. Hyperxia signaling to genes:

Alzheimer disease among elderly patients with anaemia: population-
based investigation in Olmsted county, Minnesota. Ann Epidemiol


impairment in patients presenting to a memory disorders clinic. J

Frausto PE, et al. Jugular bulb saturation and cognitive dysfunction


[10] Folstein MF, Folstein SE, McHugh PR. “Mini-Mental State”: A prati-
cal method for grading the cognitive state of patients for the clinician.

[11] Folstein MF, Folstein SE, McHugh PR. “Mini-Mental State”: A prati-
cal method for grading the cognitive state of patients for the clinician.

JR, Dartigues, et al. Incidence of dementia and major subtype in
Europe: a collaborative study of population-based cohorts. Neu-
rologic diseases in the Elderly Research Group. Neurology 2000;54:
S10–5.

[13] Iadecola C, Gurev R. Coupling pathogenic mechanisms in vas-

[14] Iyagi OJ, Westenwal RG, Kukel DL. The definition of anemia in

disease and vascular dementia. Alzheimer Dis Assoc Disord 1999;13(Suppl.

[16] Kalra RN. Comparison between Alzheimer’s disease and vascular


[18] Kurilla EM, Chertow GM, Luan JL, Yaffe K. Cognitive impair-
1863–9.

[19] Lasser LJ. Demonstrating the case that AD is a vascular dis-
[review].

MM, et al. Prevalence of dementia and major subtype in Eu-
rope: a collaborative study of population-based cohorts. Neuro-
logic diseases in the Elderly Research Group. Neurology 2000;54:
S4–9.

Evidence for association of anaemia with vascular dementia Neu-

haemoglobin declines in the elderly implications for reference in-

[23] Pironi L, Egidio M, Andruzz JP, Albu D, Nafziger J. Fac-
tors involved in the anemia of chronic disorders in elderly patients.

The influence of education on clinically diagnosed dementia inci-
dence and mortality data from the Kungsholmen Project. Arch Neu-

blood pressure and risk of dementia in the Kungsholmen project: a

[26] Rahm P. Perimenstrual anemia and reversible dementia: Strachan and

[27] Sananakar K, Swagger DE. Early diagnosis of dementia: Am Fam

LJ. Early inflammation and dementia: a 25-year follow up of the