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Anemia is associated with the progression of white matter disease in older adults with high blood pressure: the Cardiovascular Health Study

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Abstract

OBJECTIVES—To investigate whether anemia predicts worsening white matter hyperintensities (WMH) in older community-dwellers.

DESIGN—Prospective cohort study.

SETTING—Older community-dwellers.

PARTICIPANTS—One thousand eight hundred forty-six Cardiovascular Health Study (CHS) participants (mean age 73.7±4.4 years, 41% men, 15.6% African-Americans).

MEASUREMENTS—Participants had hemoglobin measured and a brain MRI in 1992–93, and a second brain MRI in 1997–98. Anemia was defined according to WHO criteria (hemoglobin <12 g/dl in women and <13 g/dl in men). Worsening WMH was determined by standardized side-by-side readings.

RESULTS—After 5 years, WMH worsened in 517 participants (28%). Progression was not associated with anemia in the whole sample, in gender- or race-strata or in other pre-specified subgroups (participants with renal dysfunction or diabetes), except in participants with high blood pressure (≥140/90 mmHg). Among the 678 participants with high blood pressure, those with anemia (10.5%) had a 1.79-fold increased risk of WMH worsening (95%CI 1.06–2.98; p for interaction between anemia and high blood pressure = 0.013), independent of demographics, baseline WMH,

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cardiovascular risk factors and comorbidities, medications, renal function, inflammation and incident stroke (logistic regression models). There was no increased risk in anemic participants with normal blood pressure.

CONCLUSION—Anemia may contribute to WMH worsening in older adults with high blood pressure.

Anemia is common among older adults,[1] and is potentially treatable. Recent investigations demonstrated cognitive impairment, in particular executive dysfunction,[2, 3] in older adults with anemia. Anemia is also associated with depressive symptoms, [4] reduced physical performance[5] and mortality.[6]

Age-related white matter hyperintensities (WMH) on brain MRI, a consequence of brain small vessels disease, are also associated with cognitive impairment, poor executive function[7] and depressive symptoms,[8] and predict physical function decline[9] and mortality in the elderly.[10] However, the relationship between anemia and WMH in older people has not been investigated.

In previous studies, anemia was associated with incident stroke in chronic kidney disease patients[11] and with cardiovascular events in diabetic chronic kidney disease patients.[12] The kidney is a target organ for hypertensive damage, and anemia may represent a marker of duration or severity of kidney disease.[13] Besides being the most important modifiable risk factor for stroke, high blood pressure (BP) is one of the main determinants of brain small vessels disease and WMH,[14, 15] likely acting through vascular remodeling, narrowing of the arteriolar lumen and impaired cerebral BP autoregulation.[16] Diabetes, which is a risk factor for kidney disease[17] and stroke,[18] may also impact on brain small vessels disease[16, 19]. Anemia could aggravate cerebral hypoxia interacting with hypoperfusion consequent to hypertensive or diabetic small vessels changes.

We investigated whether anemia independently predicted the progression of WMH as assessed by repeated MRI scans over 5 years in older community-dwelling participants to the Cardiovascular Health Study (CHS). We also a priori investigated whether the association between anemia and WMH progression would be greater in those with high BP, renal impairment or diabetes.

METHODS

Study Population

The CHS enrolled 5888 men and women 65 years or older from 4 US communities in either 1989–90 or 1992–93.[20] Exclusion criteria included being institutionalized, wheelchair-bound, or current or recent treatment forcancer. Between 1991 and 1994 and about 5 years later, participantswere invited to undergo MRI scanning. Time between the two scans varied between 3.2 and 7.5 years. The 3660participants who underwent the initial scan were healthier thanthose who were not scanned, and the 2116 participants whounderwent 2 scans were healthier than those who underwent a singlescan.[21] Each participant's pair of scans was re-read side-by-side to assess WMH change. Because of technical problems, 197of the original 2116 pairs of scans could not be re-read together. Demographics, cardiovascular diseases and risk factors were similar between the remaining 1919 participants and the excluded 197.[21] Of these 1919 participants, 1846 had a hemoglobin measurement in 1992–93, which was close in time to the initial scan, and were included in the analysis. Demographics and cardiovascular diseases and risk factors were similar for these1846 and for the 73 participants excluded because of missing hemoglobin data.

Definition of anemia

Hemoglobin concentration was measured in fasting blood samples by automated coulter counters at hematology laboratories near each field center. Internal and external quality-assurance reports were examined, and concurrently obtained duplicate samples were analyzed for 3% of participants.[22] Anemia was defined according to WHO criteria, as a hemoglobin concentration <13 g/dL in men and <12 g/dL in women.

Outcome

The MRI protocol and the reliability of the resulting readings have been extensively described elsewhere.[7] In brief, between 1991 and1994 and again 5 years later, sagittal T1-weighted localizer images and axial T1, spin-density, and T2-weighted images were acquired. Severity of WMH was graded on a visual semi-quantitative 10-point scale (0–9), with higher scores indicating greater severity. To assess the progression of WMH across the two MRIs, trained neuroradiologists read all the scans side-by-side without any knowledge about order of scans, grades from previous cross-sectional readings or clinical information on the participants. The change could potentially range from −9 (greatest possible improvement in WMH) to 9 points (greatest worsening).

Covariates

Variables considered in this analysis were those from assessment closest in time and before the initial scan.[21] Demographics included age, gender and race. For this analysis 7 participants who were not Caucasians or African-Americans were grouped with the Caucasians. Other considered covariates were WMH grade at the initial scan, time between the scans, and variables previously associated with WMH progression in this same sample:[7] smoking history (never, versus former or current smoker), diastolic BP (mmHg), dizziness upon standing, prevalent cardiovascular disease (one or more myocardial infarction, angina, congestive hearth failure or intermittent claudication before the initial scan), a history of stroke, any brain infarct at the initial MRI scan, ankle-arm index, HDL and LDL cholesterol (mg/dl), factor VII (%) and statin (HMG co-A reductase inhibitor) use. We also considered aspirin use, body mass index (kg/m^2) and inflammation, defined as any two of albumin in the bottom tertile, or C-reactive protein (CRP), white blood cell count or fibrinogen in the top tertile.[6] Incident strokes between the two scans were followed-up until July 2006.

Elevated blood pressure, diabetes and renal function

Systolic BP (mmHg), high BP (BP at the visit ≥140/90), left ventricular hypertrophy at the ECG, use of anti-hypertensive medications and diabetes (serum fasting glucose ≥126 mg/dl or specific treatment) were collected at baseline. Impaired renal function was estimated with serum cystatin C level (mg/L), a very sensitive marker of kidney dysfunction in previous CHS investigations.[23] Renal insufficiency, expressed as a creatinine level ≥1.5 mg/dl in men and ≥1.3 mg/dl in women,[6] was also considered.

Statistical analysis

Differences in hemoglobin concentration and in the prevalence of anemia between men and women were tested with Student's t-test and chi-square respectively, in the whole sample and in race strata. Similarly, Student's t-test (continuous variables) and chi-square tests (dichotomous variables) were used to compare baseline characteristics between anemic and non-anemic participants, and to assess differences in hemoglobin concentration and prevalence of anemia between participants with worsening WMH ≥ and <1 grade, in the whole sample and in race strata. Logistic regression models were used to assess the risk of worsening WMH ≥1 using either hemoglobin, anemia and other baseline variables as potential predictors.

Following the hypothesized patho-physiologic speculations on which we based the study objectives, we tested, as a pre-specified aim, the interaction between both hemoglobin and anemia and potential effect modifiers: high BP, cystatin C (continuous variable), renal insufficiency (yes/no) and diabetes (p level for significant interaction < 0.10). We also tested the interaction of hemoglobin and anemia with race, since clinically relevant differences in hemoglobin concentration among races have been demonstrated,[1, 24] and with baseline WMH grade, which, in previous CHS analyses, was an effect modifier for a number of risk factors for WMH progression.[7] We found a significant interaction between anemia and high BP. Bivariate associations between anemia and WMH progression were tested again using the chi-square test, and age-adjusted with logistic regression in BP strata. The multivariable risk of progression of WMH of at least 1 grade for participants with anemia, compared to non-anemic ones, was assessed using logistic regression models by BP strata. Demographics, baseline WMH grade and time between the scans were forced in a basic model. Anemia and other covariates were introduced with a backward procedure (deletion at p level <0.05) in separate models. These models included anemia and 1) vascular risk factors and comorbidities 2) non-invasive measures of vascular disease 3) history of stroke 4) renal function 5) inflammation 6) medications 7) incident stroke. A comprehensive final model included all the considered covariates. In sensitivity analyses, we used the absolute WMH change over 5 years as an outcome in linear regression models, in which anemia and the other covariates were introduced with the same modality used in the logistic regression.

Analyses were performed using SPSS® 14.0 (Chicago, Illinois).

RESULTS

Mean hemoglobin ± standard deviation (SD) among the 1846 included participants (mean age 73.7±4.4, 41% men, 15.6% African-Americans) was 13.7±1.3 g/dl (mean±SD). Women had lower hemoglobin than men (13.3±1.1 vs 14.4±1.3) and African-Americans had slightly lower values than others (13.5±1.2 vs 13.8±1.3). Anemia was more prevalent in African-Americans (14.2% vs 10.2%), and slightly more prevalent in men than women in both race groups (14.7% vs 14.0% in African-Americans, 12.3% vs 9.0% in the others).

Anemic participants, compared to non-anemic ones, were older and more often men and African-Americans (Table 1). Among vascular risk factors, the only differences were found in BMI and diastolic BP, which were both lower in participants with anemia. Anemic participants had more often a history of stroke. As expected, poorer renal function and inflammation were both associated with anemia at baseline. Medications, baseline WMH grade and the time between the scans were comparable between anemic and non-anemic participants (Table 1).

On follow-up MRIs, 1325 of the 1846 participants (72%) showed no change and 4 a WMH grade reduction. WMH increased 1, 2, 3 and 4 grades in 440, 67, 9 and 1 participants, respectively. Comparing these 517 (28%) participants with a WMH worsening ≥1 grade, with the 1329 (72%) with no worsening, mean hemoglobin (13.2±1.2 vs 13.3±1.1, p=0.987) and the prevalence of anemia (11.2% vs 10.9%, p=0.845) were similar. Mean hemoglobin and anemia were also comparable after stratification by gender and race. In univariate logistic regression models, worsening of WMH worsening ≥1 grade was predicted by WMH grade at the initial MRI scan (OR [95%CI]=1.13 [1.06–1.21]), MRI infarcts at baseline (1.65 [1.32–1.06]), cardiovascular risk factors (smoking and diastolic BP, OR [95%CI] of 1.40 [1.14–1.72] and 1.01 [1.00–1.02] respectively) and antihypertensive medications (OR [95%CI] of 1.32 [1.05–1.68]). Anemia did not significantly predict the WMH worsening (OR [95%CI], 1.03 [0.75–1.42]).

We tested the interaction between hemoglobin or anemia and certain baseline characteristics (high BP, renal function, diabetes, race and baseline WMH). The interaction between anemia and high BP was statistically significant (p=0.013), whereas hemoglobin or anemia did not significantly interact with other hypothesized effect modifiers. Six-hundred-seventy-eight participants had high BP (373 of them [55%] were on antihypertensive therapy). In this group, the prevalence of baseline anemia was higher among those with WMH worsening than in those without (14% versus 9%, age-adjusted p-value=0.041) (Table 2). In the group with normal baseline BP, neither the prevalence of anemia nor mean hemoglobin concentration were different comparing participants with or without worsening WMH.

Using multivariable logistic regression, the risk of worsening WMH ≥1 grade was higher for participant with high BP and anemia, compared to those without anemia, after adjustment for demographics and other covariates (Table 3). Overall, renal function and inflammation determined the greatest reduction (around 20% of the OR) of the risk of worsening WMH for anemic participants with high BP. Between the two scans, 179 participants experienced an incident or recurrent stroke. Adjustment for these events did not substantially modify the results (Table 3).

Separate linear regression models with continuous WMH change over 5 years as an outcome yielded similar results. Even adjusting for cystatin C level and inflammation, the two factors with the greatest impact on the association between anemia and WMH change in the logistic regression models, anemia independently predicted WMH worsening in high BP participants (Unstandardized Beta±SE 0.146±0.070, p=0.038 in cystatin C-adjusted model; Unstandardized Beta±SE 0.154±0.070, p=0.027 in inflammation-adjusted model). In the fully adjusted linear regression model the effect remained unchanged (Unstandardized Beta±SE 0.173±0.075, Standardized Beta 0.094, p=0.021).

DISCUSSION

In this sample of older community-dwellers, neither hemoglobin nor anemia were associated with the progression of WMH over 5 years. Participants with high BP only had an almost twofold increased risk of worsening WMH, regardless of anti-hypertensive treatment. This excess risk seemed relevant compared to the unadjusted ORs associated with other predictors, and was independent of many possible confounders.

To our best knowledge, this is the first study to investigate the effect of anemia on brain white matter disease. In previous studies, anemia was associated with physical performance decline,[5] disability,[25] and mortality.[6] These outcomes are also predicted by white matter disease.[9, 10, 26] Recent investigations have examined the relationship between anemia, defined according to the WHO criteria, and cognitive/affective status at old ages. In a cross-sectional evaluation from the Women's Health and Aging Study II, participants with anemia had worse executive function (measured with the Trail Making Test), compared to those without anemia,[3] and in the InCHIANTI study anemia was associated with depressive symptoms.[4] Finally, in an acute care setting, older adults with anemia had significantly lower global cognitive performance, compared to those with normal hemoglobin.[2] Our findings suggest that, in participants with high BP, the association of anemia with cognitive and mood disorders might be mediated by white matter disease, a well established risk factor for cognitive/executive dysfunction and depression at old ages.[7, 8]

High BP is a strong risk factor for white matter disease.[14, 15] However, in a previous CHS report,[7] the only BP variable which independently predicted WMH progression was a higher diastolic BP, whereas neither systolic BP nor hypertension did. Our results demonstrated that high BP is associated with progression of WMH, although only in combination with another

risk factor. Renal function can be affected by high BP, and this might in part justify why renal function, among the other considered covariates, had the greatest impact on the association between anemia and WMH worsening in high BP participants. In previous studies, anemia predicted incident stroke in patients with chronic kidney disease.[11, 12] Different mechanisms have been proposed to explain this association. Among other possibilities, chronic renal failure may reflect the deleterious effects of hypertension on a vascular bed other than the brain. If this were the case, the findings linking anemia to incident stroke would be consistent with our results.

Different pathophysiologic mechanisms could be suggested to explain the association between anemia and WMH in older adults with high BP. First, anemia could aggravate the chronic hypoperfusion of the white matter. Age and hypertension are the most important determinants of structural changes of small penetrating arteries and arterioles of the white matter. Such changes include thickening of the vessels wall and narrowing of the vascular lumen (arteriolosclerosis).[16] Sclerotic remodeling also impairs the ability of small vessels to dilate, so that in hypertensive patients with arteriolosclerosis, a reduced BP, of the type that occurs during cardiac dysrhythmias[16] or heart failure,[27] could lead to a decrease in blood flow. An additional factor that may impair the white matter blood flow is the tortuosity and elongation of these vessels, [16] which is related to the severity of hypertension.[28] In summary, these mechanic obstacles to white matter blood flow determined by hypertension could induce an increased sensitivity to a further reduction of oxygen supply when hemoglobin concentration is low. Another possible mechanism, which has been also invoked to explain the effect of anemia in precipitating stroke in chronic kidney disease patients, is the reduced production of erythropoietin. Besides regulating red blood cell production, erythropoietin receptors in the brain seem to have a protective effect against hypoxic/ischemic injury,[29] and a small trial in humans has shown initial limited evidence towards a positive effect of treatment with erythropoietin towards an improvement in clinical outcomes 1 months after stroke.[30] Although the association of anemia with WMH progression in hypertensive older adults was independent of renal function, the possible role of erythropoietin deficiency can not be excluded, since the adjustment for renal function reduced the strength of the association between anemia and worsening WMH.

Strengths of our study are the community-based setting, longitudinal design, large number of available covariates and the reliability of the side-by-side MRI reading. Some limitations need to be acknowledged. We had no information on cause of anemia (e.g. vitamin B12, folate or erythropoietin levels, iron studies) so could not assess potential pathways other than inflammation and renal function linking anemia to WMH progression.

Another possible limitation is the relatively small sample size after stratification: a study with a larger number of African-Americans, who are disproportionately affected by hypertension and anemia, is needed. Finally, anemia is associated with mortality in this population:[6] we can not exclude that a survivor bias could have selected participants with an exceptional resilience to cerebrovascular damage, due perhaps to intrinsic factors or lifestyle.

In summary, in this sample of older community-dwellers, anemia predicted worsening WMH over 5 years in high BP participants independent of many risk factors for WMH worsening and other possible confounders. Since anemia and, mostly, hypertension are potentially treatable conditions, further studies are needed to confirm these findings and to investigate the pathophysiologic link behind anemia and WMH.

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Table 1

Baseline characteristics of the whole sample and by anemia status.

		WHO Anemia		
	Total sample	**NO**	**YES**	
	N=1846	**N=1643 (89%)**	**N=203 (11%)**	**p-value***
Age	73.7±4.4	73.6±4.4	74.8±4.8	<0.001
Men	758 (41.1)	662 (40.3)	96 (47.3)	0.056
African-Americans	288 (15.6)	247 (15.0)	41 (20.2)	0.056
Body Mass Index (kg/m2)	26.6±4.2	26.7±4.2	25.6±4.1	0.001
Diabetes	158 (8.6)	135 (8.2)	23 (11.3)	0.138
Current/former smoker	932 (51.6)	829 (51.6)	103 (51.8)	0.963
Systolic blood pressure (mm hg)	134.3±20.0	134.4±20.1	133.1±19.0	0.353
Diastolic blood pressure (mm hg)	71.1±10.9	71.5±11.0	67.7±9.7	<0.001
High blood pressure	687 (32.2)	616 (37.5)	71 (35.0)	0.484
Dizziness	40 (2.2)	37 (2.3)	3 (1.5)	0.478
Left ventricular hypertrophy by ECG	69 (3.8)	63 (3.9)	6 (3.0)	0.525
Ankle-arm blood pressure	1.1±0.2	1.1±0.2	1.1±0.1	0.229
LDL (mg/dl)	127.4±31.9	127.9±32.0	123.7±35.1	0.083
HDL (mg/dl)	54.1±14.7	54.3±13.8	53.3±13.6	0.380
Factor VII %	110.9±25.0	111.0±24.0	109.7±24.0	0.480
Prevalent cardiovascular diseases	335 (18.1)	297 (18.1)	38 (18.7)	0.620
History of stroke	52 (2.8)	41 (2.5)	11 (5.4)	0.018
History of TIA	36 (2.0)	29 (1.8)	7 (3.4)	0.102
Cystatin C (mg/L)	1.05±0.24	1.04±0.22	1.15±0.34	<0.001
Inflammation	710 (38.5)	607 (36.9)	103 (50.7)	<0.001
Any lipid lowering medication	147 (8.0)	134 (8.2)	13 (6.4)	0.382
Aspirin use	649 (35.2)	586 (35.7)	63 (31.0)	0.188
Antihypertensive medications	825 (44.7)	729 (44.4)	96 (47.3)	0.438
WMH grade at the initial MRI scan	1.8±1.4	1.8±1.4	1.9±1.5	0.339
WMH grade >1 at the initial MRI scan	930 (50.4)	819 (49.8)	111 (54.7)	0.194
Infarcts at the initial MRI scan	496 (26.9)	444 (27.0)	52 (25.6)	0.669
Time between the MRI scans, years	5.0±0.6	5.0±0.6	5.0±0.7	0.766

*Non-anemic Vs anemic participants

WMH: white matter hyperintensities.

High blood pressure: blood pressure ≥ 140/90; prevalent cardiovascular diseases any myocardial infarction, angina, congestive hearth failure or claudication; inflammation: any 2 among an albumin concentration in the bottom tertile, or C-reactive protein, white blood cell count or fibrinogen in the top tertile.

Table 2

Prevalence of anemia between participants with white matter hyperintensities (WMH) change ≥1 grade and those with no WMH change. Analyses are stratified by blood pressure (defined as measured blood pressure values <140/90 – normal blood pressure –, vs ≥140/90 –high blood pressure; p for interaction of anemia and high BP = 0.013).

	WMH change ≥1 grade		Age-adjusted p-value
	No	Yes	
Normal BP, N=1168	**N = 850 (72.8%)**	**N = 318 (27.2%)**	
Anemia (WHO), N (%)	102 (12.0)	30 (9.4)	0.133
High BP, N=678	**N = 479 (70.6%)**	**N = 199 (29.4%)**	
Anemia (WHO), N (%)	43 (9.0)	28 (14.1)	0.041

BP: blood pressure

WHO criteria for anemia: hemoglobin <12 g/dl (women) or <13 g/dl (men).

Table 3

Risk of worsening white matter hyperintensities (WMH) ≥1 grade in anemic participants with and without high blood pressure (measured blood pressure ≥140/90), compared to non-anemic ones. Multivariable logistic regression models.

	Model Adjustment Factors*	OR (95%CI) for WMH change ≥1 grade	
		BP < 140/90 N=1168	BP ≥ 140/90 N=678
A	Demographics	0.74 (0.48–1.15)	1.69 (1.03–2.82)
B	A + Baseline WMH grade and time between scans	0.75 (0.48–1.16)	1.74 (1.04–1.92)
C	B + Vascular risk factors and comorbidities	0.77 (0.49–1.21)	1.83 (1.07–3.15)
D	B + Measures of vascular disease	0.70 (0.44–1.11)	1.84 (1.08–3.06)
E	B + History of stroke	0.74 (0.48–1.14)	1.70 (1.02–3.29)
F	B + Cystatin C	0.72 (0.46–1.14)	1.60 (1.01–2.70)
G	B + Inflammation	0.74 (0.48–1.17)	1.59 (1.01–2.83)
H	B + Medications	0.73 (0.47–1.13)	1.69 (1.01–2.82)
I	B + Incident stroke	0.76 (0.49–1.18)	1.68 (1.02–2.83)
	Fully adjusted	0.68 (0.41–1.10)	1.79 (1.03–2.98)

* Models are adjusted for the following variables:

A. Age, gender and race.

B. Model A + baseline WMH grade and time between the scans.

C. Model B + body mass index, diabetes, smoking status (current/past Vs. never), LDL, HDL, dizziness, factor VII and prevalent cardiovascular diseases.

D. Model B + ankle-arm index, left ventricular hypertrophy by ECG

E. Model B + history of stroke

F. Model B + Cystatin C

G. Model B + inflammation (at least two of: low albumin, high CRP, white blood cells, fibrinogen)

H. Model B + lowering-lipid medications, antihypertensive medications and aspirin use.

I. Model B + strokes between the two MRI scans.

Fully adjusted: adjusted for all the above mentioned covariates.