ORIGINAL ARTICLE

Anemia in young patients with ischaemic stroke

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Background and purpose: To investigate the association of anemia on admission with ischaemic stroke (IS), stroke severity and early functional outcome in patients with cervical artery dissection (CeAD) or with IS of other causes (non-CeAD-IS patients).

Methods: The study sample comprised all patients from the Cervical Artery Dissection and Ischaemic Stroke Patients (CADISP) study without pre-existing disability and with documentation of stroke severity and hemoglobin (Hb) concentration on admission. Anemia was classified as mild (Hb < 12 g/dl in women and Hb < 13 g/dl in men) or moderate to severe (Hb < 10 g/dl in women and Hb < 11 g/dl in men). Stroke severity on admission was assessed with the National Institutes of Health Stroke Scale (NIHSS). Outcome after 3 months was assessed with the modified Rankin Scale (mRS-3mo). Unfavorable outcome was defined as mRS-3mo ≥ 3.

Results: Amongst 1206 study patients (691 CeAD and 515 non-CeAD), 87 (7.2%) had anemia, which was moderate to severe in 18 (1.5%) patients. Anemia was associated with female sex in both study samples, but no further associations with risk factors or comorbidities were observed. In CeAD patients, anemia was associated with occurrence of stroke ($P = 0.042$). In both study samples, anemic patients had more severe strokes (CeAD, $P = 0.023$; non-CeAD, $P = 0.005$). Functional outcome was not associated with anemia in general, but moderate to severe anemia was significantly associated with unfavorable outcome ($P = 0.004$).

Conclusion: Anemia on admission was associated with stroke in CeAD patients and with more severe strokes in both study samples. Moderate to severe anemia may predict unfavorable outcome.

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Introduction

Anemia, a global health problem affecting a substantial part of the world's population, is associated with increased morbidity and mortality. In patients with acute ischaemic stroke (IS), anemia has been reportedly associated with more severe strokes and less favorable

EUROPEAN JOURNAL OF NEUROLOGY

outcome [1–10]. The mechanisms of anemia-related morbidity and mortality in most stroke patients are complex and multifactorial. Anemia results in reduced oxygen transport capacity, but also induces alterations in blood coagulation, blood viscosity and cerebral vasodilatation [11,12]. Moreover, it may be a bystander of stroke-associated conditions such as higher age, hypertension, hypercholesterolemia, diabetes, smoking or renal insufficiency [3]. Comorbidities in the – mostly elderly – IS patients are potentially confounding variables, which render it challenging to explain the association of anemia with IS occurrence, stroke severity and functional outcome after IS.

Patients with cervical artery dissection (CeAD) and patients with IS due to causes different from CeAD from the Cervical Artery Dissection and Ischaemic Stroke Patients (CADISP) study were analyzed. This study sample of young patients was chosen to reduce the confounding effects of age and comorbidities. Comorbidities were particularly rare in the large subgroup of patients with CeAD [13]. CeAD is a major cause of IS in patients <50 years, but CeAD may also entail purely local symptoms only. The mechanism of CeAD is largely unknown, but a multifactorial etiology with environmental as well as constitutional risk factors seems likely [13–15]. Patients with a pre-morbid disability [modified Rankin Scale (mRS) > 0] were excluded. In the current study the associations between anemia on admission, stroke occurrence, stroke severity and outcome after 3 months were explored.

Methods

Patients

The CADISP consortium enrolled 983 CeAD patients and 658 patients with IS from other causes (non-CeAD-IS patients) evaluated in neurological departments across 18 centers in eight countries [14]. Non-CeAD-IS patients were matched to CeAD patients according to age and sex. For the current study, 79 patients with documented disability (mRS > 0) before onset of symptoms and 81 patients with missing documentation of pre-morbid disability were excluded. Amongst the 1481 remaining patients, hemoglobin (Hb) concentration from a blood sample drawn within 24 h after admission was missing in 178 patients, and stroke severity on admission (assessed by the National Institutes of Health Stroke Scale – NIHSS) in 137 patients. The final study sample (n = 1206) comprised 691 CeAD patients (median age 44 years; range 13–75) and 515 non-CeAD-IS patients (median age 45 years; range 17–70).

Anemia was defined according to the World Health Organization as Hb < 12 g/dl in women and Hb < 13 g/dl in men. Moderate to severe anemia was defined as Hb < 10 g/dl in women and Hb < 11 g/dl in men. The following standardized variables were derived from the CADISP clinical database as was done in previous research [13,15–17]: age, sex, patient group (CeAD versus non-CeAD), vascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, current smoking) according to pre-defined criteria [13], body mass index, prior mechanical trigger events [15], previous infection, prior disability (defined as mRS > 0) before onset of stroke or CeAD, type of presenting symptom (IS and transient ischaemic attack [16,17]), stroke severity as assessed by the NIHSS score, plasma concentration of hemoglobin (g/dl), time between symptom onset and first day of hospitalization with determination of the laboratory findings (diagnostic delay) [17] and history of any of the following major vascular events: stroke (any), CeAD, peripheral artery disease, coronary heart disease and aortic aneurysm or aortic dissection. Finally, 3-month follow-up was assessed with the mRS score [16]. Outcome after 3 months (mRS-3mo) was considered as unfavorable for mRS-3mo ≥ 3. CeAD patients without stroke were excluded from the analysis of outcome after 3 months.

Statistical analysis

For each analyzed item, the number of patients with missing values is indicated. Data with normal distribution are presented as mean ± standard deviation (SD), non-normally distributed data as median and range (min, max). For categorical variables counts and percentages are given. Data were compared with the chi-squared test, Mann–Whitney test or Student's t test, respectively. A two-sided P value of <0.05 was considered as statistically significant. Binary logistic regression models were used to analyze the association between anemia and stroke severity or stroke occurrence after adjustment for age, sex and stroke etiology (CeAD versus non-CeAD) or between anemia and outcome after adjustment for age, sex, stroke etiology and stroke severity. Statistical analysis was performed with the Statistical Package for the Social Sciences, SPSS (SPSS Inc., IBM Corporation, Somers, NY, USA; 21.0 for Windows).

Ethics

The CADISP study protocol (http://clinicaltrials.gov/ct2/show/NCT00657969) was approved by competent local authorities of all participating centers and is conducted according to the national rules concerning ethics committee approval and informed consent.

Results

The final study sample (n = 1206) comprised 691 CeAD patients and 515 non-CeAD-IS patients (Table 1). IS occurred in 422 of the CeAD patients. Patients were classified as non-anemic (n = 1119) or anemic (n = 87). In both study groups (CeAD patients and non-CeAD-IS patients) anemia was more frequent in women (P = 0.049 and $P < 0.001$, respectively) and was associated with more severe strokes (higher NIHSS on admission) (P = 0.023 and P = 0.005; Table 1). In the CeAD group which comprised patients with or without stroke, anemia was associated with stroke occurrence (P = 0.042). Diagnostic delay, defined as delay between onset of symptoms and hospitalization (blood sampling for laboratory tests was always performed on the first day of hospitalization), differed between CeAD patients (median delay 3 days; range 0−107) and non-CeAD-IS patients (median delay 0 days; range 0−32; $P < 0.001$), but not between anemic and non-anemic patients. No association of anemia with vascular risk factors, comorbidities or diagnostic delay was observed. In our study samples, no association of anemia with early functional outcome was apparent (Table 1).

Amongst the eligible patients with IS and with documented early functional outcome, 13 had moderate to severe anemia (defined as Hb < 10 g/dl in women and Hb < 11 g/dl in men; Table 2). Patients with moderate to severe anemia were more likely to have unfavorable outcome (mRS-3mo ≥ 3) compared to the other patients (including those with mild anemia and those without anemia). In a logistic regression model with outcome as dependent variable, moderate to severe anemia was a significant predictor for unfavorable outcome (P = 0.004), independently from stroke severity and age.

Discussion

Our study in a large sample of young non-disabled patients yielded the following key findings: (i) anemia on admission was associated with stroke severity in IS patients from both study groups (CeAD and non-CeAD); (ii) anemic CeAD patients were more likely to have cerebral ischaemia than non-anemic ones; (iii) moderate to severe anemia on admission was an independent predictor of unfavorable outcome after 3 months, but mild anemia had no impact on outcome in our sample.

Pathophysiological considerations on the mechanisms behind these findings remain speculative due to the retrospective study design with a lack of imaging and neuromonitoring data. Former small clinical studies and results from animal models suggest that on the one hand oxygen transport failure in the penumbra due to lower Hb levels might be responsible for reduced oxygen extraction fraction and infarction. On the other hand changes in blood viscosity due to lower Hb and hematocrit levels might counteract this mechanism by improving cerebral perfusion. With respect to outcome after stroke most studies suggest a higher Hb level or intermediary Hb levels and a U-shaped correlation to predict favorable outcome. However, further prospective trials are needed to address this topic in a more accurate way. In most patients in this study, anemia was mild with Hb levels far above accepted critical thresholds for blood transfusion or brain ischaemia [18]. Nevertheless significant associations of anemia with stroke occurrence and stroke severity were observed. In our study sample, anemia was not associated with unfavorable early functional outcome. A minority of the patients presented with more severe anemia. These patients were older and presented with more severe strokes. Unfavorable functional outcome was more likely in this small sample of patients with moderate to severe anemia, and this association remained significant and strong after adjustment for age and stroke severity.

A large sample of young non-disabled patients was chosen for this study. Contrary to findings in study samples of older stroke patients [1], anemia was not associated with vascular risk factors or comorbidities in this population. Our findings indicate that low Hb levels increase the risk for stroke, for more severe strokes and for unfavorable outcome.

Our study has several limitations. As blood samples were taken only once during the first 24 h after admission, the possible influence of the exact timing and management measures (further spontaneous drop, effect of volume expansion or blood draws) and their effect on IS and early recovery/deterioration could not be analyzed. Due to lack of information, a possible influence of women's menopausal status on Hb levels could not be addressed. The power of our study was restricted, since only a minority of the analyzed patients (n = 80; 7.2%) were anemic and few amongst them had moderate to severe anemia, which was mainly attributed to the young age of the study population and to the exclusion of patients with any pre-morbid disability from the analysis. However, the choice of exclusion criteria might have biased our findings. Additional laboratory data (C-reactive protein values, white blood cell counts, hematocrit) were not available for a substantial number of study patients. Thus, the questions of underlying mechanisms and whether these variables may have confounded our findings could not be addressed and it was not possible to distinguish between different types of anemia.

Table 1 Study sample of CeAD and non-CeAD-IS patients with and without anemia

		CeAD patients (n = 691)					Non-CeAD-IS patients (n = 515)				
	Missing	No anemia	Anemia	P*	OR	95% CI*	No anemia	Anemia	P*	OR	95% CI*
n (%)		643 (93.1)	48 (6.9)					476 (92.4)	39 (7.6)		
Age	(0/0)	44.0 ± 10.1	43.3 ± 9.6	0.621			44.5 ± 10.5	41.5 ± 9.1	0.089		
Female sex	(0/0)	266 (41.4)	27 (56.3)	**0.049**			178 (37.4)	28 (71.8)	**< 0.001**		
Hypertension	(4/0)	166 (26.0)	10 (20.8)	0.536	0.79	0.38–1.66	172 (36.1)	13 (33.3)	0.577	1.25	0.57–2.74
Diabetes	(2/0)	14 (2.2)	1 (2.1)	0.892	1.15	0.15–9.17	35 (7.4)	2 (5.1)	0.944	1.06	0.23–4.80
Hypercholesterolemia	(11/3)	113 (17.9)	9 (18.8)	0.698	1.17	0.54–2.54	138 (29.1)	10 (26.3)	0.836	1.09	0.50–2.36
Current smoking	(5/2)	178 (27.9)	14 (29.2)	0.759	1.11	0.58–2.12	220 (46.4)	18 (46.2)	0.916	1.04	0.53–2.02
Body mass index	(30/13)	24.4 ± 3.7	24.8 ± 4.3	0.239	1.05	0.97–1.13	26.0 ± 4.8	23.7 ± 3.2	0.053	0.92	0.84–1.00
Prior trauma	(8/3)	266 (41.9)	12 (25.0)	**0.027**	0.47	0.24–0.92	50 (10.5)	4 (10.5)	0.849	0.90	0.30–2.71
Prior infection	(11/4)	128 (20.2)	8 (17.0)	0.577	0.80	0.36–1.76	49 (10.4)	7 (18.4)	0.120	2.04	0.83–5.01
Hx vascular events	(17/8)	19 (3.0)	2 (4.3)	0.596	1.50	0.33–6.77	71 (15.2)	7 (17.9)	0.221	1.76	0.71–4.32
Diagnostic delay	(25/13)	3 (0–93)	3 (0–107)	0.273	1.01	0.99–1.04	0 (0–31)	0 (0–32)	0.756	0.98	0.87–1.11
Stroke	(0/0)	386 (60.0)	36 (75.0)	**0.042**	2.01	1.03–3.95					
Stroke/TIA	(0/0)	471 (73.3)	43 (89.6)	**0.023**	3.00	1.16–7.74					
Stroke severity	(0/0)	3 (0–25)	5.5 (0–33)	**0.023**	1.05	1.01–1.10	2 (0–40)	5 (0–27)	**0.005**	1.07	1.02–1.13
Favorable outcome	(12/49)	316 (83.8)	26 (78.8)	0.554	0.73	0.26–2.08**	381 (88.4)	29 (82.9)	0.844	1.14	0.32–4.07**

CaAD, cervical artery dissection; non-CeAD-IS, ischaemic stroke from other causes; OR, odds ratio; CI, confidence interval; Hx, history of; TIA, transient ischaemic attack. Missing shows the number of patients with CeAD/non-CeAD-IS with missing data for the analyzed item; stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) on admission; outcome after 3 months was assessed by the modified Rankin Scale (mRS-3mo); unfavorable outcome was defined as outcome with mRS-3mo > 2; diagnostic delay (duration between onset of symptoms and admission to the hospital with blood sampling for laboratory tests) was measured in days. Groups were compared with t test and chi-squared test (P) and in a logistic regression model to adjust for age and sex (P*) or for age, sex and stroke severity (NIHSS) on admission (**). In the CeAD group, stroke severity on admission (assessed by the NIHSS score) and early functional outcome (assessed by the modified Rankin Scale) was only analyzed in patients with ischaemic stroke (n = 422). Significant test results were shown as bold values.

Table 2 Predictors of early functional outcome

	Unfavorable outcome $n = 124$	Favorable outcome $n = 752$	P	P*	OR (95% CI)*
Female sex	39 (31.5)	327 (43.5)	0.014	0.126	148 (0.90–2.24)
Age	46.7 ± 9.0	43.7 ± 10.7	0.001	0.011	0.97 (0.95–0.99)
Etiology (CeAD versus non-CeAD)	68 (54.8)	342 (45.5)	0.065	0.531	0.86 (0.54–1.38)
NIHSS on admission	14 (0–40)	2 (0–24)	<0.001	<0.001	0.81 (0.78–0.84)
Moderate to severe anemia	8 (6.7)	5 (0.7)	<0.001	0.004	0.12 (0.03–0.51)

Patients with stroke from both study groups (CeAD and non-CeAD-IS) were analyzed. Groups were compared with the chi-squared test (female sex, etiology, moderate to severe anemia), t test (age) or Mann–Whitney test (NIHSS on admission). All variables were analyzed in a logistic regression model with outcome as dependent variable. For each predictor P values (P*), odds ratios (OR) and 95% confidence intervals (95% CI)* were calculated.

Conclusion

In a large study sample of young patients, anemia was associated with occurrence of stroke and stroke severity. A secondary analysis of patients with moderate to severe anemia suggested that more severe anemia was associated with unfavorable outcome.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

References

1. Huang WY, Chen IC, Meng L, Weng WC, Peng TI. The influence of anemia on clinical presentation and outcome of patients with first-ever atherosclerosis-related ischemic stroke. *J Clin Neurosci* 2009; **16:** 645–649.
2. Kimberly WT, Wu O, Arsava EM, *et al*. Lower hemoglobin correlates with larger stroke volumes in acute ischemic stroke. *Cerebrovasc Dis Extra* 2011; **1:** 44–53.
3. Sico JJ, Concato J, Wells CK, *et al*. Anemia is associated with poor outcomes in patients with less severe ischemic stroke. *J Stroke Cerebrovasc Dis* 2013; **22:** 271–278.
4. Zakai NA, Katz R, Hirsch C, *et al*. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort. The Cardiovascular Health Study. *Arch Intern Med* 2005; **165:** 2214–2220.
5. Leal-Noval SR, Munoz-Gomez M, Murillo-Cabezas F. Optimal hemoglobin concentration in patients with subarachnoid hemorrhage, acute ischemic stroke and traumatic brain injury. *Curr Opin Crit Care* 2008; **14:** 156–162.
6. Wade JP, Taylor DW, Barnett HJ, Hachinksi VC. Hemoglobin concentration and prognosis in symptomatic obstructive cerebrovascular disease. *Stroke* 1987; **18:** 68–71.
7. Bahtia RS, Garg RK, Gaur SPS, *et al*. Predictive value of routine hematological and biochemical parameters on 30-day fatality in acute stroke. *Neurol India* 2004; **52:** 220–223.
8. Kellert L, Martin E, Sykora M, *et al*. Cerebral oxygen transport failure?: decreasing hemoglobin and hematocrit levels after ischemic stroke predict poor outcome and mortality: STroke: RelevAnt Impact of hemoGlobin, Hematocrit and Transfusion (STRAIGHT) – an observational study. *Stroke* 2011; **42:** 2832–2837.
9. Kellert L, Herweh C, Sykora M, *et al*. Loss of penumbra by impaired oxygen supply? Decreasing hemoglobin levels predict infarct growth after acute ischemic stroke: Stroke: Relevant Impact of Hemoglobin, Hematocrit and Transfusion (STRAIGHT) – an observational study. *Cerebrovasc Dis Extra* 2012; **2:** 99–107.
10. Tanne D, Molshatzki N, Merzeliak O, Tsabari R, Toashi M, Schwannenthal Y. Anemia status, hemoglobin concentration and outcome after acute stroke: a cohort study. *BMC Neurol* 2010; **10:** 22.
11. Hare GM, Tsui AK, McLaren AT, Ragoonanan TE, Yu J, Mazer CD. Anemia and cerebral outcomes: many questions, fewer answers. *Anesth Analg* 2008; **107:** 1356–1370.
12. Tsui AK, Dattani ND, Marsden PA, *et al*. Reassessing the risk of hemodilutional anemia: some new pieces to an old puzzle. *Can J Anaesth* 2010; **57:** 779–791.

13. Debette S, Metso TM, Pezzini A, *et al*. Association of vascular risk factors with cervical artery dissection and ischemic stroke in young adults. *Circulation* 2011; **123:** 1537–1544.
14. Debette S, Metso TM, Pezzini A, *et al*. CADISP-genetics: an international project searching for genetic risk factors of cervical artery dissections. *Int J Stroke* 2009; **4:** 224–230.
15. Engelter ST, Grond-Ginsbach C, Metso TM, *et al*. Cervical artery dissection: trauma and other potential mechanical trigger events. *Neurology* 2013; **80:** 1950–1957.
16. Engelter ST, Dallongeville J, Kloss M, *et al*. Thrombolysis in cervical artery dissection – data from the Cervical Artery Dissection and Ischaemic Stroke Patients (CADISP) database. *Eur J Neurol* 2012; **19:** 1199–1206.
17. Lichy C, Metso A, Pezzini A, *et al*. Predictors of delayed stroke in patients with cervical artery dissection (CeAD). *Int J Stroke* 2015; **10:** 360–363.
18. Weiskopf RB, Kramer JH, Viele M, *et al*. Acute severe isovolemic anemia impairs cognitive function and memory in humans. *Anesthesiology* 2000; **92:** 1646–1652.

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