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Elevated peripheral leukocyte counts in acute cervical artery dissection

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Background and purpose: It has been suggested that inflammation may play a role in the development of cervical artery dissection (CeAD), but evidence remains scarce.

Methods: A total of 172 patients were included with acute (< 24 h) CeAD and 348 patients with acute ischaemic stroke (IS) of other (non-CeAD) causes from the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study, and 223 age- and sex-matched healthy control subjects. White blood cell (WBC) counts collected at admission were compared across the three groups.

Results: Compared with healthy control subjects, CeAD patients and non-CeAD stroke patients had higher WBC counts ($P < 0.001$). Patients with CeAD had higher WBC counts and were more likely to have WBC > 10 000/μl than non-CeAD stroke patients (38.4% vs. 23.0%, $P < 0.001$) and healthy controls (38.4% vs. 8.5%, $P < 0.001$). WBC counts were higher in CeAD (9.4 ± 3.3) than in IS of other causes (large artery atherosclerosis, 8.7 ± 2.3; cardioembolism, 8.2 ± 2.8; small vessel disease, 8.4 ± 2.4; undetermined cause, 8.8 ± 3.1; $P = 0.022$). After adjustment for age, sex, stroke severity and vascular risk factors in a multiple regression model, elevated WBC count remained associated with CeAD, as compared with non-CeAD stroke patients [odds ratio (OR) = 2.56; 95% CI 1.60–4.11; $P < 0.001$) and healthy controls (OR = 6.27; 95% CI 3.39–11.61; $P < 0.001$).

Conclusions: Acute CeAD was associated with particularly high WBC counts. Leukocytosis may reflect a pre-existing inflammatory state, supporting the link between inflammation and CeAD.

Introduction

Little is known about the etiology of cervical artery dissection (CeAD), a major cause of IS in young people [1]. Both genetic and environmental factors are likely to be involved [2]. Among environmental factors, several studies have shown that infections and inflammation are common during the week before the onset of CeAD symptoms, and these factors have been considered as putative trigger factors of CeAD [3,4]. In addition, imaging studies have revealed signs of local inflammation around the affected vessels of patients with spontaneous internal carotid artery dissection (ICAD) but not in those with traumatic ICAD [5,6], suggesting that inflammation is not merely reactive, but plays a causative role in the etiology of spontaneous dissections. However, studies including

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healthy control subjects are scarce and only a few used biological tests to assess systemic inflammation.

White blood cell (WBC) count is a simple and widely used laboratory marker associated with inflammation, but it is of limited specificity due to interaction with a variety of other factors, including smoking, age, body mass index (BMI), ethnicity, or steroid treatment. In patients with acute IS, increased leukocyte counts were associated with stroke severity and infarct size [7]. Elevated WBC count is an independent predictor of unfavorable outcome in patients with IS [8–10], myocardial infarction [11,12] and peripheral arterial disease [13].

The aim of the present study was to analyze WBC counts as a marker of inflammation in patients with acute CeAD. WBC counts from CeAD and non-CeAD IS patients from the multicenter Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study were analyzed and compared with findings from healthy control subjects.

Methods

The methods of the CADISP study have been described elsewhere [14]. The study protocol was approved by relevant local authorities in all participating centers and was conducted according to the national rules concerning ethics committee approval and informed consent.

Patients in the CeAD and non-CeAD IS groups were recruited in the same centers. The primary aim of the CADISP consortium was to perform a genetic association study to identify genetic susceptibility factors of CeAD. All but two centers also participated in a clinical study including detailed screening of putative environmental risk factors and clinical and radiological characteristics using a standardized questionnaire. The CADISP clinical study comprises 983 CeAD patients and 658 patients with strokes of other (non-CeAD) etiologies. For the present study, hospital-based control groups of sex- and age-matched (with CeAD patients) healthy Caucasian subjects ($n = 223$) were recruited in Heidelberg ($n = 82$), Ludwigshafen ($n = 86$) and Brescia ($n = 55$). Control subjects visited the centers for an interview. Baseline characteristics and vascular risk factors were recorded and a peripheral venous blood sample was taken. Subjects with a history of stroke or of CeAD were excluded from the control group.

Hypertension was defined by a history of elevated blood pressure (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) diagnosed by the treating physician or use of a blood pressure–lowering therapy. Hypercholesterolemia was defined as a fasting total cholesterol ≥ 6.20 mmol/l or low-density lipoprotein cholesterol ≥ 4.1 mmol/l, measured within 48 h after admission to the hospital or diagnosed by the treating physician, or use of a cholesterol-lowering therapy. Diabetes mellitus was defined as a history of diabetes mellitus diagnosed by the treating physician with a fasting glucose > 7 mmol/l or use of an antidiabetic therapy. An infection in the week preceding the dissection was defined by the presence of at least one typical symptom of infection (e.g. cough, flu-like illness, vomiting, diarrhea, purulent sputum), in combination with fever (temperature $\geq 38°C$), or the presence of at least one typical symptom of infection with corresponding serologic, cultural, or radiologic findings indicating an acute infection, or the combination of at least two typical corresponding symptoms. Trauma was defined as physical impact on the head or neck (e.g. extreme neck movements, cervical manipulation, lifting heavy loads) less than 1 month prior to the CeAD. With regard to stroke at admission, patients were classified into the following 'stroke severity' categories: no ischaemia, transient ischaemic attack (TIA) including transient monocular blindness, mild stroke with National Institutes of Health Stroke Scale (NIHSS) 0–3, moderately severe stroke with NIHSS 4–15, or severe stroke with NIHSS > 15.

Patients with blood samples collected within the first day of onset of symptoms ($n = 569$) were included in the current study. Among the selected patients, stroke severity at admission assessed by the NIHSS was available for 520 patients (172 with CeAD and 348 with non-CeAD IS). For a comparison between included and excluded patients, see Table S1. The non-CeAD patients were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [15] into five categories: large artery atherosclerosis (LAA, $n = 44$), cardioembolism (CE, $n = 134$), small vessel disease (SVD, $n = 25$), other determined etiology (OD, $n = 10$) and undetermined etiology (UND, $n = 135$).

White blood cell counts ($\times 1000$ cells/μl $\pm$ SD) were assessed at admission for CeAD and non-CeAD IS patients. Leukocytosis was defined as leukocyte counts $> 10 \times 10^3/\mu$l).

Differences between groups were assessed by chi-squared test or Fisher's exact test for categorical variables, by Student's *t*-test and one-way ANOVA for continuous variables, and by Mann–Whitney or Kruskal–Wallis test for variables with a non-normal distribution. Multiple logistic regression analysis was used to assess the association between CeAD and leukocytosis, adjusting for age and sex as well as for all variables with significant differences ($P < 0.05$) in univariate analysis. Analyses were done using the SPSS

19.0 statistics software package (IBM Corporation, Somers, NY, USA).

Results

White blood cell counts from acute CeAD patients (9.4 ± 3.3; ×1000 cells/μl ± SD) and acute non-CeAD IS patients (8.6 ± 2.8) were significantly higher than in healthy controls (6.8 ± 1.9; Table 1). CeAD patients were more likely to have leukocytosis than non-CeAD IS patients (38.4% vs. 23.0%, $P < 0.001$) and healthy controls (8.5%, $P < 0.001$). In comparison with non-CeAD IS patients, and after adjustment for age, sex, stroke severity, current smoking and infections or trauma prior to onset of symptoms, smoking, BMI, hypertension, hypercholesterolemia, diabetes mellitus and coronary heart disease, the association between CeAD and high WBC counts [odds ratio (OR) = 1.09, 95% CI 1.02–1.16 for 1000 leukocyte increase] or WBC > 10×10^3 (OR = 2.56; 95% CI 1.60–4.11) remained significant (Table 1). In comparison with healthy controls, and after adjustment for age, sex, BMI, hypertension, smoking and infections, the OR was 6.27 (95% CI 3.39–11.61).

White blood cell counts and prevalence of leukocytosis according to etiologic subgroups are shown in Fig. 1. WBC counts were higher in CeAD (9.4 ± 3.3) than in stroke of any non-CeAD cause (LAA, 8.7 ± 2.3; CE, 8.2 ± 2.8; SVD, 8.4 ± 2.4, UND, 8.8 ± 3.1; $P = 0.022$). WBC counts in patients with ICAD (9.4 ± 3.5) or vertebral artery dissection (9.5 ± 3.0) were not different ($P = 0.79$).

In CeAD patients, increased leukocyte count was significantly associated with stroke severity ($P = 0.017$) and young age ($P = 0.022$) and non-significantly associated with BMI ($P = 0.06$) and female sex ($P = 0.09$), as shown in multiple logistic regression analysis (Table 2). CeAD patients were more likely to report infections during the week prior to the acute event, mostly infections of the upper and lower respiratory tract (Table 1). Neither a history of preceding infections nor trauma or infections were associated with increased WBC counts (Table 2).

Discussion

In our study population, acute CeAD patients were more likely to have elevated WBC counts than non-CeAD IS patients (of any etiology) and healthy controls. The relation was independent from potential confounders like stroke severity, BMI, diabetes mellitus, smoking or coronary heart disease.

Earlier studies suggested a causative role for inflammation in the etiology of CeAD, but studies including healthy control subjects were scarce and few used biological tests to assess systemic inflammation. Post-acute C-reactive protein levels are elevated in CeAD [16]. A small study found that WBC counts and C-reactive protein were elevated in acute spontaneous CeAD, but not in traumatic CeAD [17]. In the present

Table 1 Baseline characteristics of the population. Note that female sex, body mass index (BMI) and white blood cell (WBC) count are reported as means (SD); stroke severity is reported as median (range); other variables are reported as numbers (%)

	CeAD (n = 172)	non-CeAD (n = 348)	Controls (n = 223)	P_{global}	CeAD versus non-CeAD			
					P_{crude}	OR (95% CI)	$P_{multivar.}$	OR (95% CI)
Female sex	64 (37.2)	136 (39.1)	88 (39.5)	0.89	0.68	0.92 (0.63–1.35)	0.16	0.73 (0.47–1.14)
Age	43.8 ± 9.8	44.6 ± 10.3	44.2 ± 13.5	0.74	0.41	0.99 (0.98–1.01)	0.09	1.02 (1.00–1.04)
Stroke severity	2 (0–4)	2 (2–4)	0	< 0.001	< 0.001	0.69 (0.56–0.86)	**0.008**	0.71 (0.55–0.91)
Trauma	59 (34.7)	37 (10.7)	n.a.		< 0.001	4.45 (2.78–7.04)	**< 0.001**	3.67 (2.20–6.11)
Infection	33 (19.4)	35 (10.2)	9 (4.1)	< 0.001	0.004	2.13 (1.27–3.56)	**0.018**	2.04 (1.13–3.69)
URT infection	24 (14.1)	19 (5.5)			0.003	2.66 (1.41–5.03)	n.a.	
LRT infection	6 (3.5)	5 (1.5)			0.14	2.47 (0.74–8.20)	n.a.	
Current smoking	62 (36.5)	153 (44.2)	67 (30.6)	0.004	0.09	0.72 (0.50–1.06)	0.08	0.68 (0.44–1.05)
BMI	24.9 ± 4.0	25.9 ± 4.7	25.4 ± 4.8	0.06	0.019	0.95 (0.91–0.99)	0.13	0.96 (0.91–1.01)
HTN	45 (26.3)	127 (36.5)	46 (21.0)	< 0.001	0.021	0.62 (0.42–0.93)	0.27	0.75 (0.45–1.25)
Hchol	33 (19.5)	98 (28.4)	38 (17.8)	0.007	0.031	0.61 (0.39–0.96)	0.26	0.74 (0.43–1.25)
Diabetes mellitus	3 (1.7)	25 (7.2)	12 (5.5)	0.036	0.017	0.23 (0.07–0.77)	**0.035**	0.19 (0.04–0.88)
Coronary heart disease	2 (1.2)	11 (3.2)	0	0.017	0.19	0.36 (0.08–1.64)	0.38	0.38 (0.05–3.28)
WBC count	9.4 ± 3.3	8.6 ± 2.8	6.8 ± 1.9	< 0.001	0.004	1.09 (1.03–1.16)	n.a.	
WBC > 10	66 (38.4)	80 (23.0)	19 (8.5)	< 0.001	< 0.001	2.09 (1.40–3.10)	**< 0.001**	2.56 (1.60–4.11)

OR, odds ratio; HTN, hypertension; HChol, hypercholesterolemia; URT, upper respiratory tract; LRT, lower respiratory tract; n.a., not applicable; P_{global}, test results of comparison of CeAD, non-CeAD and control groups under the null-hypothesis of no difference between the three groups. Stroke severity was categorized as follows: 0, no ischaemia; 1, transient ischaemic attack (TIA) or transient monocular blindness, but no stroke; 2, mild stroke with National Institutes of Health Stroke Scale (NIHSS) 0–3; 3, stroke with NIHSS 4–15; 4, severe stroke with NIHSS > 15.

Bold values indicate significant findings in multivariate analyses.

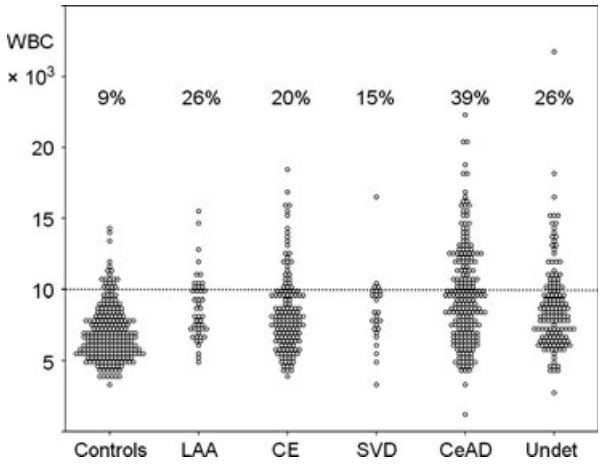

Figure 1 Scatterplot of white blood cell (WBC) counts in the study samples. Percentages of patients with WBC > 10 000 cells are indicated on top of each sample. LAA, large artery atherosclerosis; CE, cardioembolism; SVD, small vessel disease; CeAD, cervical artery dissection; Undet, undetermined etiology.

study, previous trauma or previous infections were not associated with leukocyte counts. In contrast to the previous studies, the analyzed blood samples in this study were taken within 24 h after onset of symptoms, in order to minimize the possible effect of post-stroke infections or stroke-induced immunosuppresion [18] on WBC counts. In IS patients with previous infections, higher total leukocytes counts were found than in patients without previous infections [19]. In our study sample, WBC counts from CeAD patients with previous infections were not higher than those from patients without infections prior to the acute event. No explanation was found for this unexpected result. As the incidence of infection in CeAD and non-CeAD IS patients in our study (19.4% vs. 10.2%) was much lower than in previous studies (58.1% vs. 32.8% [3]; 31.9% vs. 13.5% [4]) it is speculated that infectious diseases with minor signs were incompletely reported in the multicenter CADISP study, or that initial studies may have been biased towards extreme findings because of small sample sizes and regression effect [20].

It is proposed that the high WBC counts in acute CeAD indicate an inflammatory state that pre-exists the onset of the acute event. Our findings are in line with recent imaging studies, which revealed signs of local inflammation around the affected vessels of patients with CeAD, but not in those with traumatic CeAD [5,6]. Inflammation may play an important role in the disintegration of the arterial wall. It cannot be excluded that the morphological alterations of the connective tissue from CeAD patients may be secondary to inflammatory processes, as was reported in a mouse model of Marfan syndrome. The aortic wall of newborn Marfan is normal, but medial degeneration develops within the first weeks after birth, accompanied by inflammatory infiltration. Defective components of the extracellular matrix appear to be potent attractants for macrophage chemotaxis in *in vitro* experiments [21–23]. These findings suggest that inflammation on top of constitutional connective tissue defects may increase the risk for disintegration of the arterial wall upon CeAD.

There are several potential limitations of this study. First, in patients with CeAD, the very moment of the dissection event is difficult to determine. Minor mural lesions may have developed and may have induced an early inflammatory response, before a genuine arterial

Table 2 Factors associated with development of leukocytosis upon acute cervical artery dissection (CeAD). Note that female sex, body mass index (BMI) and white blood cell (WBC) count are reported as means (SD); stroke severity is reported as median (range); other variables are reported as numbers (%)

	WBC ≤ 10 × 10^3 (n = 106)	WBC > 10 × 10^3 (n = 66)	P_{crude}	OR (95% CI)	$P_{multivar.}$	OR (95% CI)
Female sex	36 (34.0)	28 (42.4)	0.27	1.43 (0.76–2.70)	0.09	1.91 (0.90–4.06)
Age	44.8 ± 9.9	42.4 ± 9.6	0.13	0.98 (0.95–1.01)	**0.022**	0.96 (0.93–0.99)
Stroke severity	2 (0–4)	3 (0–4)	**0.03**	1.37 (1.03–1.82)	**0.017**	1.57 (1.08–2.26)
Trauma	37 (35.2)	22 (33.8)	0.85	0.94 (0.49–1.80)	0.80	1.10 (0.51–2.39)
Infection	23 (21.9)	10 (15.4)	0.30	0.65 (0.29–1.47)	0.39	0.66 (0.26–1.69)
Current smoking	37 (35.6)	25 (37.9)	0.76	1.10 (0.58–2.09)	0.85	1.07 (0.52–2.25)
Migraine	39 (37.1)	17 (26.3)	0.14	0.60 (0.30–1.18)	0.12	0.54 (0.25–1.18)
BMI	24.6 ± 3.5	25.4 ± 4.7	0.23	1.05 (0.97–1.14)	0.06	1.10 (1.00–1.21)
HTN	27 (25.5)	18 (27.7)	0.75	1.12 (0.56–2.25)	1.00	1.00 (0.42–2.39)
Hchol	19 (18.1)	14 (21.9)	0.55	1.27 (0.59–2.75)	0.46	1.42 (0.56–3.59)
ICAD/VAD	60/44	36/30	0.69	1.14 (0.61–2.12)	0.13	1.80 (0.84–3.84)
Multiple CeAD	13 (12.3)	2 (3.0)	0.06	0.24 (0.05–1.07)	0.10	0.29 (0.06–1.27)

OR, odds ratio; HTN, hypertension; HChol, hypercholesterolemia; ICAD, internal carotid artery dissection; VAD, vertebral artery dissection. Univariate and multivariate analysis in a multiple regression model were used to identify stroke severy and age as the only factors that are independently associated with leukocytosis. Importantly, preceding trauma and infections were not associated with leukocytosis.
Bold values indicate significant findings.

dissection (sudden splitting up of the vascular wall and intramural hemorrhage) occurred [24]. Moreover, since CeAD may occur without any symptoms [25], onset of symptoms might be preceded by an asymptomatic stage. Hence, although all analyzed blood samples were collected within 24 h after symptom onset, earlier unnoticed vessel wall damage may have triggered an inflammatory response. Secondly, although the data were from a large international database, our final study sample was relatively small, because only CeAD patients within 24 h after symptom onset were included. Nevertheless, there was enough statistical power in this study to detect the association. Thirdly, as patients with severe symptoms are more likely to be admitted to the hospital within 24 h, our study sample was biased towards patients with more severe stroke (Table S1). Notably, CeAD patients without ischemia were under-represented in our study sample. However, our findings remained significant after adjustment for stroke severity. A final limitation of our study was the exclusion of other inflammatory markers, such as C-reactive protein, erythrocyte sedimentation rate and temperature, due to differences in laboratory standardizations (C-reactive protein) and incomplete data (erythrocyte sedimentation rate, temperature at admission). However, despite these limitations, it is believed that our results support a pathophysiological link between CeAD and acute systemic inflammation. In future studies it will be analyzed whether elevated WBC counts upon acute CeAD are associated with unfavorable outcome.

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Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Comparison of included and non-included patients from the CADISP database.

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Appendix 1
CADISP investigators

Belgium: Departments of Neurology, Erasmus University Hospital, Brussels and Laboratory of Experimental Neurology, ULB, Brussels, Belgium (Shérine Abboud, Massimo Pandolfo); Leuven University Hospital and Vesalius Research Center (VIB), Leuven, Belgium (Vincent Thijs). *Finland:* Department of Neurology: Helsinki University Central Hospital (Tiina Metso, Antti Metso, Turgut Tatlisumak). *France:* Departments of Neurology, Lille University Hospital-EA2691 (Marie Bodenant, Stéphanie Debette, Didier Leys, Paul Ossou), Sainte-Anne University Hospital, Paris (Fabien Louillet, Jean-Louis Mas, Emmanuel Touzé), Pitié-Salpêtrière University Hospital, Paris (Sara Leder, Anne Léger, Sandrine Deltour, Sophie Crozier, Isabelle Méresse, Yves Samson), Amiens University Hospital (Sandrine Canaple, Olivier Godefroy, Chantal Lamy), Dijon University Hospital (Yannick Béjot, Maurice Giroud), Besancon University Hospital (Pierre Decavel, Elizabeth Medeiros, Paola Montiel, Thierry Moulin, Fabrice Vuillier); Inserm U744, Pasteur Institute, Lille (Philippe Amouyel, Jean Dallongeville, Stéphanie Debette). *Germany:* Departments of Neurology, Heidelberg University Hospital (Caspar Grond-Ginsbach, Manja Kloss, Christoph Lichy, Tina Wiest, Inge Werner, Marie-Luise Arnold), University Hospital of Ludwigshafen (Michael Dos Santos, Armin Grau); University Hospital of München (Martin Dichgans); Department of Dermatology, Heidelberg University Hospital (Ingrid Hausser); Department of Rehabilitation: Schmieder-Klinik, Heidelberg (Tobias Brandt, Constanze Thomas-Feles, Ralf Weber). *Italy:* Departments of Neurology: Brescia University Hospital (Elisabetta Del Zotto, Alessia Giossi, Irene Volonghi, Alessandro Padovani, Alessandro Pezzini), Perugia University Hospital (Valeria Caso), Milano University Hospital (Anna Bersano, Silvia Lanfranconi, Pierluigi Baron), Monza University Hospital (Simone Beretta, Carlo Ferrarese), Hospital Milano San Raffaele (Maria Sessa, Giacomo Giacolone); Department of Rehabilitation: Santa Lucia Hospital, Roma (Stefano Paolucci). *Switzerland:* Department of Neurology, Basel University Hospital (Stefan Engelter, Felix Fluri, Florian Hatz, Dominique Gisler, Annet Tiemessen, Margareth Amort, Philippe Lyrer). *UK:* Clinical Neuroscience, St George's University of London (Hugh Markus). Non-European countries: *Turkey:* Department of Neurology, University Hospital of Istanbul (Ayse Altintas). *Argentina:* Department of Neurology, University Hospital Sanatorio Allende, Cordoba. (Juan Jose Martin).