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ORIGINAL COMMUNICATION

Towards understanding seasonal variability in cervical artery dissection (CeAD)

Manja Kloss · Antti Metso · Alessandro Pezzini · Didier Leys · Maurice Giroud · Tiina M. Metso · Turgut Tatlisumak · Christoph Lichy · Anna Bersano · Shérine Abboud · Armin Grau · Philippe A. Lyrer · Stéphanie Debette · Jean Dallongeville · Juan Martin · Valeria Caso · Caspar Grond-Ginsbach · Stefan T. Engelter

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Abstract Cervical artery dissection (CeAD) occurs more often in autumn or winter than in spring or summer. We searched for clinical variables associated with this seasonality by comparing CeAD patients with onset of symptoms in autumn–winter (September 22–March 21) versus those with first CeAD symptom in spring–summer (March 22–September 21). We performed a cross-sectional study using data from the multicenter CADISP (Cervical Artery Dissection and Ischemic Stroke Patients) registry. Age- and sex-matched patients with ischemic stroke attributable to a cause other than CeAD (non-CeAD patients) were analyzed to study the specificity of our findings. Autumn–winter CeAD patients had a higher median brachial pulse pressure at admission (55 vs. 52 mmHg; $p = 0.01$) and more recent infections (22.0% vs. 16.6%; $p = 0.047$), but prevalence of trauma was not associated with seasonal onset. Multivariable logistic regression analysis revealed that higher pulse pressure was significantly associated with autumn–winter CeAD ($p = 0.01$), while age, gender, history of hypertension, recent infection, and recent trauma were not. No association between pulse pressure and seasonal occurrence was found in non-CeAD ischemic stroke patients. Increased pulse pressure was associated with the higher frequency of CeAD in autumn or winter.

Keywords Seasonal variability · Cervical artery dissection · Blood pressure

Introduction

Cervical artery dissection (CeAD) is a common cause of ischemic stroke in young adults [1]. CeAD was reported to occur more often in autumn [2] or winter [3, 4]. The reason of this seasonality remains unclear [2, 4]. It has been speculated that the seasonal variation of infection [2–4], (mild) trauma [5], or blood pressure [4, 6, 7] might matter. A seasonal pattern with a preference in autumn or winter has been also reported for stroke due to other causes [8], but findings were contradictory [9]. Thus, it remains to be shown whether the reported seasonal pattern in CeAD is characteristic for CeAD.

We used the databank of the multicenter Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) consortium. The aim of our explorative study was to compare patients with onset of CeAD in autumn or winter versus those with symptom onset in spring or summer with regard to variables possibly related to the seasonal pattern (i.e., recent infections, recent trauma, and blood pressure indices) and assess whether variation in one of these variables might be associated with seasonal onset of CeAD. A second aim of our study was to show the specificity of this association by analyzing seasonal onset of stroke among non-CeAD patients.

C. Grond-Ginsbach and S.T. Engelter contributed equally to this work.

For the CADISP Group.

Members of the CADISP group are given in the Appendix.

M. Kloss (✉) · A. Metso · A. Pezzini · D. Leys · M. Giroud · T. M. Metso · T. Tatlisumak · C. Lichy · A. Bersano · S. Abboud · A. Grau · P. A. Lyrer · S. Debette · J. Dallongeville · J. Martin · V. Caso · C. Grond-Ginsbach · S. T. Engelter
Department of Neurology, University of Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany
e-mail: Manja.Kloss@med.uni-heidelberg.de

Methods

The CADISP consortium aimed at exploring genetic [10] and environmental risk factors [11] and treatment aspects of CeAD. For the CADISP clinical study, we included consecutive patients evaluated in a department of neurology with a diagnosis of CeAD or non-CeAD ischemic stroke patients across 18 centers in 8 countries [11]. The diagnosis of CeAD was based on widely accepted diagnostic criteria [11]. The CADISP clinical database comprises a total of 983 CeAD patients and 658 non-CeAD patients, which were frequency-matched by age (by 5 years intervals) and gender to CeAD patients in the same centers. Almost all patients had symptom onset between 1999 and 2009; a small number of patients (<4%), ascertained through registries of CeAD patients previously established in some of the recruiting centers, had a qualifying event before 1999. The recruitment period was identical for CeAD and non-CeAD patients and covers all seasons in the same proportions. For the purpose of the current cross-sectional study, CeAD patients (and non-CeAD ischemic stroke patients) were dichotomized according to the date of symptom onset. Autumn–winter patients comprised all patients with onset of symptom occurring between September 22 and March 21. Patients with first symptoms between March 22 and September 21 were labeled spring–summer patients. Patients with missing date of symptom onset and those from the only country of the southern hemisphere (Argentina, $n = 16$) were excluded. The following standardized variables were used from the CADISP database: age, gender, vascular risk factors according to predefined criteria [11], site of dissection (i.e., internal carotid artery, vertebral artery, both arteries), type of presenting symptom (ischemic symptoms (i.e., ischemic stroke or TIA) vs. non-ischemic symptoms (i.e., Horner syndrome, cranial nerve palsy, tinnitus, headache and cervical pain), recent trauma, recent infection, hypertension and initial blood pressure values applying the following definitions. A recent trauma was defined as cervical trauma occurring ≤1 month prior to the CeAD. If the trauma prompted a visit to a physician or hospitalization, the trauma was considered major. All other forms of traumas were considered mild. We diagnosed a recent infection as reported [3]. Briefly, diagnosis required at least one typical clinical symptom in combination with fever or corresponding serological, cultural, or radiological findings indicating an acute infection. In addition, combinations of at least two typical clinical corresponding symptoms were accepted. The first blood pressure measured at admission was recorded. We defined hypertension: (1) as a history of elevated blood pressure (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) diagnosed by the treating physician or (2) use of blood pressure lowering therapy. We distinguished systolic blood pressure (SBP), diastolic blood pressure (DBP), and brachial pulse pressure (PP) which was defined as the difference between the SBP and DBP.

Statistical analyses

The dichotomized patient groups were compared using non-parametric Mann–Whitney test, χ^2 and Fisher exact tests. Data were given as mean and standard deviation (±SD) or median with interquartile range (IQR) where appropriate, respectively. Multivariable logistic regression was used to assess the association of seasonal occurrence with recent infection [2, 4], recent trauma [4], and blood pressure indices [4] adjusted for the following predefined variables: "age", "gender", and "type of presenting symptom" (ischemic symptoms vs. non-ischemic symptoms) as well as any additional variable which reached significance in the univariable analysis. Onset of symptoms in spring–summer or in autumn–winter was defined as outcome variable for the regression analysis.

Ethics

The CADISP study protocol was approved by relevant local authorities in all participating centers and is conducted according to the national rules concerning ethics committee approval and informed consents [10].

Results

A total of 960 out of 983 (98%) CeAD patients and 646 out of 658 (98%) non CeAD ischemic stroke patients were eligible for this study. Ten (1.0%) CeAD and 9 (1.4%) non-CeAD ischemic stroke patients were excluded, because time of onset of symptoms was not documented. CeAD patients did not differ from non-CeAD ischemic stroke patients in mean age (44.0 ± 10.0 vs. 44.5 ± 10.5; $p = 0.32$) and gender (56.9 vs. 61.1% male, $p = 0.10$). CeAD occurred more often in the autumn or winter (56.3%) than in spring or summer (43.7%; $p = 0.007$) which was observed in each recruiting country. No seasonal preference was observed among non-CeAD ischemic stroke patients (48.0 vs. 52.0%; $p = 0.50$).

Autumn–winter CeAD patients had a higher median brachial pulse pressure (55 vs. 52 mmHg; $p = 0.01$) and more recent infections (22.0 vs. 16.6%; $p = 0.047$) than spring–summer CeAD patients. No other variables including recent trauma, age, site of dissection, presenting symptom, body mass index (BMI), or vascular risk factors differed between both groups (Table 1).

Multivariate regression analysis revealed that brachial pulse pressure was significantly associated with seasonal

Table 1 Comparison of characteristics of CeAD patients with symptom onset in autumn–winter versus those with onset in spring–summer

	Autumn–winter CeAD	Spring–summer CeAD	*p* value	Odds ratio [95% CI]
Number (%)	540 (56.3%)	420 (43.7%)	**0.007**	
Demographics				
Gender (male) (%)	321 (59.4%)	225 (53.6%)	0.08	1.27 [0.98–1.64]
Age (mean ± SD)	44.0 ± 9.8	44.1 ± 10.3	0.83	
Environmental factors				
Preceding infections	117 (22.0%)	68 (16.6%)	**0.047**	1.41 [1.01–1.97]
Preceding minor trauma	212 (39.9%)	170 (41.1%)	0.74	0.95 [0.73–1.24]
Preceding severe trauma	30 (5.6%)	16 (3.8%)	0.20	1.56 [0.84–2.90]
Blood pressure indices				
SBP median (IQR)	140 (28)	136.5 (30)	0.057	
DBP median (IQR)	80 (23)	80 (22)	0.97	
PP median (IQR)	55 (17)	52 (20)	**0.010**	
Hypertension	138 (25.8%)	107 (25.7%)	1.00	1.01 [0.75–1.35]
Risk factors				
Hypercholesterol	105 (19.8%)	71 (17.2%)	0.36	1.19 [0.85–1.66]
Diabetes mellitus	8 (1.5%)	11 (2.6%)	0.25	0.56 [0.22–1.40]
Current smoking	141 (26.5%)	120 (28.7%)	0.47	0.90 [0.67–1.19]
Migraine	205 (38.4%)	151 (36.4%)	0.54	1.09 [0.84–1.42]
BMI (mean ± SD)	24.5 ± 3.8	24.5 ± 4.1	0.99	
Presenting symptom				
Stroke/TIA	426 (78.9%)	330 (78.6%)	0.94	1.02 [0.75–1.39]
Non-ischemic[b]	114 (21.1%)	90 (21.4%)		
Site of dissection				
Carotid artery	339 (62.7%)	266 (63.3%)	1.02	1.02 [0.79–1.33]
Vertebral artery	182 (33.7%)	140 (33.3%)	0.98	1.27 [0.75–1.29]
Both	19 (3.5%)	14 (3.3%)	0.95	1.27 [0.47–1.91]
Recruiting countries			0.41	
Belgium	18 (51.4%[a])	17 (48.6%[a])		
Finland	92 (52.9%[a])	82 (47.1%[a])		
France	185 (58.9%[a])	129 (41.1%[a])		
Germany	97 (52.2%[a])	89 (47.8%[a])		
Italy	95 (59.7%[a])	64 (40.3%[a])		
Switzerland	51 (56.7%[a])	39 (43.3%[a])		
Turkey	2 (100%[a])	0 (0.0%[a])		

BMI body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *CI* confidence interval, *IQR* interquartile range, *PP* brachial pulse pressure: difference between systolic and diastolic blood pressure measured at admission [11], *SD* standard deviation

[a] Percentage per country,
[b] Non-ischemic symptoms include Horner's syndrome, cranial nerve palsy, tinnitus

Bold values indicate statistically significant ($p < 0.05$)

occurrence. No association of pulse pressure with onset in autumn–winter season was observed among patients with non-CeAD ischemic stroke (Table 2).

Discussion

The observation of an elevated incidence of CeAD in the cold half of the year was observed in earlier studies. Among 361 patients from Bern and Zurich (Switzerland), CeAD occurred significantly more often in winter than in other seasons [4]. Among 200 patients from Rochester, Minnesota, 69 CeADs occurred in autumn and 113 CeADs (56.5%) in autumn or winter [2]. Our study confirmed this CeAD preference for autumn or winter. More importantly and toward understanding seasonality, we revealed that (1) neither recent infections nor recent minor trauma were associated with seasonality in CeAD, but that (2) autumn–winter CeAD patients had higher brachial pulse pressure values than spring–summer patients. Among non-CeAD stroke patients, no such difference was observed.

Our observation about the absence of a relationship between infection and seasonal onset is in contrast to findings from an earlier case control study of 43 CeAD patients and 58 non-CeAD ischemic stroke patients [3]. CeAD in autumn or winter was associated with infections in that study, after careful adjustment for coughing, sneezing, or vomiting as possible explanatory variables. Moreover, the

Table 2 Variables predicting autumn–winter occurrence of CeAD and onset of non-CeAD ischemic stroke in autumn–winter

	CeAD		Non-CeAD ischemic stroke	
	p value	Odds ratio [95% CI]	*p* value	Odds ratio [95% CI]
Gender (male)	0.12	0.79 [0.58–1.06]	0.52	1.12 [0.80–1.56]
Age (year)	0.08	0.99 [0.97–1.00]	0.78	1.00 [0.98–1.02]
Recent infection	0.10	1.36 [0.94–1.97]	0.51	1.19 [0.71–2.00]
Recent trauma	0.24	0.84 [0.62–1.13]	0.14	0.68 [0.40–1.14]
PP (pro 1 mmHg)	**0.010**	**1.014 [1.003–1.024]**	0.33	1.01 [0.99–1.02]
Hypertension	0.26	0.82 [0.59–1.16]	0.09	0.72 [0.49–1.05]
Presenting symptom[a]	0.69	1.07 [0.76–1.53]	n.a.	

PP brachial pulse pressure, *SBP* systolic blood pressure, *n.a.* not applicable

[a] Stroke/TIA versus non-ischemic symptoms

Bold values indicate statistically significant ($p < 0.05$)

authors found significantly higher prevalence of infectious diseases in their cohorts of patients [3]. We have no convincing explanation for these differences. Our observation that infectious diseases, albeit more common in autumn–winter CeAD, were no independent determinant of autumn–winter onset was counterintuitive for the following reasons. First, bacterial and viral infections, particularly respiratory tract infections are more common in winter and autumn [12, 13]. Second, recent infections [3, 14, 15] and (trivial) traumas [5, 15] are considered as trigger factors for CeAD. Third, recent infections [2, 4] and (trivial) trauma such as those during winter sports activities [4] were assumed to possibly contribute to the seasonality of CeAD. Thus, in this context our findings may suggest that infections and (mild) trauma might be related to CeAD occurrence but not to CeAD seasonality.

Pulse pressure values were independently associated with CeAD occurrence in autumn or winter. The difference between the systolic and the diastolic blood pressures, known as pulse pressure, describes the amplitude of the blood pressure curve [16]. In aortic dissection, the intimal injury is reported to be initiated by high systolic blood pressure [16]. In addition, elevated pulse pressure values were reported to facilitate propagation of aortic dissection [16]. Blood pressure values are known to be higher in the cold season than spring and summer [6]. Aortic dissection also occurs preferentially in autumn–winter [17, 18]. In addition, the seasonal peak in occurrence of aortic dissection was related to the seasonally higher blood pressure values [19]. Such a relationship had yet to be shown for CeAD. Interestingly, Paciaroni and colleagues hypothesized that "elevated blood pressure values may thus trigger vessel rupture in spontaneous CeAD as in spontaneous aortic dissection, especially in winter" [4]. Thus, our observations supported this hypothesis, given that hypertension was shown to be associated with an increased risk of CeAD [11]. In addition, our findings suggested that the in particular, higher pulse pressure values seem to be associated with the preferential occurrence of CeAD in autumn or winter rather than in the spring or summer.

Strengths and limitations

This is the largest study addressing seasonal variability in CeAD patients to date, which enabled us to study the seasonal distribution of several variables potentially involved in seasonality of CeAD occurrence. In addition, we tested for the specificity of our results by comparing CeAD patients with a large comparison group of non-CeAD ischemic stroke patients [2, 4]. More importantly, we explored the significance of all those variables assumed to be possibly related to seasonality in previous research [2–4] (i.e., recent infection, trauma and blood pressure indices) by applying standardized and strict criteria. Nevertheless, we are aware of several limitations. First, the CADISP database has not been designed to determine the prevalence of CeAD or non-CeAD strokes. In addition, a portion of the patients was recruited retrospectively and start of the recruitment period was not identical in all centers. These limitations are unlikely to falsify our key findings as we focused on the understanding of the seasonality, which (i.e., the seasonal preference for autumn–winter) has already been reported by others [2, 4], and because the recruitment period covered CeAD and non-CeAD patients across all seasons equally. While in CeAD patients onset in autumn or winter was more frequent than onset in spring or summer, such a difference was absent in non-CeAD patients, which were recruited in the same centers over the same time period as the CeAD patients. Nevertheless, our findings should be considered exploratory and solely hypothesis-generating. Second, the recruiting centers were located in seven European countries which differ to some degree in climatic aspects. In this context, it is noteworthy that autumn–winter preference

observed for the entire study population was present in all countries studied separately (as well as in previous European and US centers [2, 4]). Third, patient recruitment was hospital-based and information about seasonal variation in traveling habits was not available. However, the absence of a seasonal preference among the age-matched control group may serve as an argument against the presence of a relevant referral bias.

In conclusion, in this large explorative study, the magnitude of the pulse pressure, rather than recent infections or recent traumas seemed to be related to the preferred onset of CeAD in autumn or winter.

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Conflicts of interest None.

Appendix

CADISP investigators

Argentina: Department of Neurology, University Hospital Sanatorio Allende, Cordoba: (Juan Jose Martin). *Belgium:* Departments of Neurology, Erasmus University Hospital, Brussels and Laboratory of Experimental Neurology, ULB, Brussels, Belgium (Shérine Abboud, Massimo Pandolfo); Leuven University Hospital (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), Besançon 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), Milan University Hospital (Anna Bersano, Silvia Lanfranconi, Pierluigi Baron), University of Milano Bicocca, San Gerardo Hospital, Monza, Italy (Simone Beretta, Carlo Ferrarese), Milan Scientific Institute San Raffaele University Hospital (Maria Sessa, Giacomo Giacalone); Department of Rehabilitation: Santa Lucia Hospital, Rome (Stefano Paolucci). *Switzerland:* Department of Neurology, Basel University Hospital (Stefan Engelter, Felix Fluri, Leo Bonati, Florian Hatz, Dominique Gisler, Margareth Amort, Philippe Lyrer,). *UK:* Clinical Neuroscience, St George's University of London (Hugh Markus). *Turkey:* Department of Neurology, University Hospital of Istanbul (Ayse Altintas).

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