Predictors of delayed stroke in patients with cervical artery dissection

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Background Stroke in patients with acute cervical artery dissection may be anticipated by initial transient ischemic or nonischemic symptoms.
Aim Identifying risk factors for delayed stroke upon cervical artery dissection.
Methods Cervical artery dissection patients from the multicenter Cervical Artery Dissection and Ischemic Stroke Patients study were classified as patients without stroke ($n = 339$), with stroke preceded by nonstroke symptoms (delayed stroke, $n = 244$), and with stroke at onset ($n = 382$). Demographics, clinical, and vascular findings were compared between the three groups.
Results Patients with delayed stroke were more likely to present with occlusive cervical artery dissection ($P < 0.001$), multiple cervical artery dissection ($P = 0.031$), and vertebral artery dissection ($P < 0.001$) than patients without stroke. No differences were observed in age, smoking, arterial hypertension, hypercholesterolemia, migraine, body mass index, infections during the last week, and trauma during the last month, but patients with delayed stroke had less often transient ischemic attack ($P < 0.001$) and local signs (Horner syndrome and cranial nerve palsy; $P < 0.001$).
Conclusions Occlusive cervical artery dissection, multiple cervical artery dissection, and vertebral artery dissection were associated with an increased risk for delayed stroke. No other risk factors for delayed stroke were identified. Immediate cervical imaging of cervical artery dissection patients without ischemic stroke is needed to identify patients at increased risk for delayed ischemia.
Key words: carotid artery dissection, multiple dissection, occlusive dissection, risk factors, stroke, vertebral artery dissection

Introduction

An arterial dissection is a longitudinal splitting up of an arterial wall associated with an intramural haemorrhage. It can occur as a spontaneous event in all large- and medium-sized arteries. Dissection of the internal carotid artery or of the vertebral artery [cervical artery dissection (CeAD)] manifests with cerebral and retinal ischemia, local signs (LS) (i.e. Horner syndrome and caudal cranial nerve palsy), pain (i.e. cervical pain and headache), or other symptoms such as tinnitus or intracranial bleeding. These symptoms can occur alone or in any combination (1). Patients without cerebral ischemia may develop neurological deficit several days after the onset of symptoms (2) or may remain free of stroke. To the best or our knowledge, risk factors for the occurrence of delayed stroke in CeAD patients were not systematically investigated. Internal

carotid artery dissection (ICAD) causing occlusion or high-grade stenosis was associated with an increased risk for immediate or delayed stroke (3). In a series of patients with vertebral artery dissections (VADs), stroke was more common in men, in patients with increasing age, and in smokers (4). In the current cross-sectional study, we aim at identifying risk factors for delayed stroke in CeAD patients without stroke at the first day of symptoms.

Methods

Cervical artery dissection patients from the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) database were used for this analysis. The structure and methods of the CADISP study have been described previously (5,6). All procedures were approved by ethics committees and other authorities at each participating center according to local rules. For the current analysis, we selected 965 patients with documentation of (i) date of onset of first symptoms of CeAD, (ii) date of onset of stroke, and (iii) date of admission to the hospital. Eighteen patients were excluded because of incomplete data.

The following variables were included in the analysis: age; gender; presence of stroke or transient ischemic attack (TIA); presence of LSs (Horner syndrome or cranial nerve palsy), pain (headache or neck pain), and affected artery; presence of occlusion of affected artery based on ultrasonography, computed tomography angiography, or magnetic resonance imaging; history of arterial hypertension (systolic blood pressure >140 or diastolic blood pressure >90), hypercholesterolemia, and diabetes mellitus; history of migraine according the International Headache Society criteria (7); mild trauma in the month preceding the onset of symptoms; infections during the week preceding the onset of symptoms; body mass index (BMI); and history of smoking.

Patients were classified in three groups: (i) patients without stroke; (ii) patients with appearance of stroke symptoms one or more days after onset of nonstroke symptoms; and (iii) patients with stroke on the day of onset of symptoms. Differences between the study groups were tested by Fisher's exact test for categorical variables and by Student's *t*-test for continuous variables, with a normal distribution (age and BMI) regarding a two-tailed *P*-value <0·05 as significant. For comparison of delay between groups, we used the Mann–Whitney *U*-test. Logistic regression analysis was used to adjust odds ratios for delay. The SPSS 17.0 statistics software package (IBM, SPSS, Chicago, IL) was used for all statistical analyses.

Results

In our study sample of 965 CeAD patients, 626 patients presented with ischemic stroke. Among the stroke patients, 244 subjects developed stroke with a delay of one or several days after the onset of symptoms (delayed stroke, 25·3%), whereas 382 patients presented with stroke on the day of onset of symptoms (immediate stroke, 39·6%). Most patients with delayed stroke came to the hospital after having developed stroke, but 13 patients suffered stroke after admission (two patients suffered stroke under antiplatelet drugs and 10 under anticoagulation with heparin).

Patients with delayed stroke were less likely to present with LSs ($P < 0.001$) or TIA ($P < 0.001$) and more likely to present with pain ($P < 0.001$) compared with patients without stroke (Table 1). Arterial imaging revealed a higher rate of occlusive dissection ($P < 0.001$), of multiple dissections ($P = 0.031$), and of VAD ($P < 0.001$) in patients with delayed stroke compared with patients that remained free of stroke. Age, gender, and putative risk factors for CeAD were not associated with increased risk for delayed stroke. Patients with immediate stroke had less pain ($P > 0.001$), less often multiple CeAD ($P > 0.001$), and less often migraine ($P < 0.006$) than patients with delayed stroke.

Patients with VAD and with ICAD were analyzed separately in Table 2. Both occlusive VAD and occlusive ICAD were associated with delayed stroke, as well as multiple VAD.

Discussion

In our study sample, stroke occurred in 64·9% of the patients, similar to 58·9% in another large sample (8). Our analysis focused on patients with delayed stroke, i.e. with stroke that was preceded by pain, TIA, or local symptoms. We identified three risk factors for delayed stroke: occlusive CeAD, multiple CeAD, and VAD.

Earlier studies compared nonstroke and stroke patients, irrespective of the occurrence of preceding nonischemic symptoms. Baumgartner and coworkers showed that patients with spontaneous ICAD with vessel occlusion or high-grade stenosis were more likely to suffer cerebral or retinal ischemic events (3). Our study confirmed that occlusive ICAD was associated with higher prevalence of delayed stroke and extended this finding for occlusive VAD. In an analysis of 186 consecutive patients with spontaneous VAD, ischemic events were more common in men, older patients, and smokers (4). In the current analysis of delayed stroke in VAD patients from the CADISP study sample, patients were not more often male. Moreover, the distribution of smoking or other putative risk factors was not different between CeAD patients with delayed stroke or without stroke.

Patients with delayed stroke had less often LSs, TIA, or pain. In our opinion, these inverse associations do not imply that patients with LSs, TIA, or pain have a lower risk to develop stroke. We assume that patients without symptoms or with mild and transient symptoms were underrepresented in the study sample because their diagnosis was missed in many cases. This assumption implies that the absolute risk for ischemic complications in CeAD patients without stroke at onset of symptoms is unknown. Our study demonstrated that patients with occlusive CeAD, with VAD, and with multiple CeAD were more likely to develop delayed stroke. However, patients with ischemic stroke are supposed to be recognized to a large part, whereas it is unclear to which extent CeAD patients without stroke were diagnosed and enrolled in this study. Unfortunately, we have no systematic observations to measure the extent of recognition bias in study samples of patients with CeAD.

Table 1 CeAD patients analyzed in this study

	No stroke (n = 339)	Delayed stroke (n = 244)	Stroke at onset (n = 382)	No stroke vs. delayed stroke — P	No stroke vs. delayed stroke — OR [95% CI]	Delayed stroke vs. stroke at onset — P	Delayed stroke vs. stroke at onset — OR [95% CI]**	No stroke at onset vs. stroke at onset — P	No stroke at onset vs. stroke at onset — OR [95% CI]**
Age	44·3 ± 9·8	43·1 ± 9·9	44·6 ± 9·9	0·14	0·067	0·23			
Male gender (%)	189 (55·8)	127 (52·0)	229 (59·9)	0·40	0·86 [0·62–1·20]	0·078	0·74 [0·53–1·03]	0·11	0·80 [0·61–1·05]
Delay onset – admission*	6 (12)	5 (8)	0 (3)	0·57	**<0·001**	**<0·001**			
Presenting signs and symptoms									
Local signs (%)	175 (51·6)	41 (16·8)	72 (18·8)	**<0·001**	0·19 [0·13–0·28]	0·71	1·09 [0·71–1·67]	**<0·001**	0·41 [0·30–0·56]
Pain (%)	294 (86·7)	227 (93·0)	240 (62·8)	**0·015**	2·04 [1·13–3·67]	**<0·001**	0·11 [0·06–0·19]	**<0·001**	0·17 [0·12–0·25]
TIA (%)	117 (34·5)	27 (11·1)	53 (13·9)	**<0·001**	0·24 [0·15–0·37]	0·27	1·33 [0·80–2·19]	**<0·001**	0·48 [0·34–0·69]
Vascular pathology									
Multiple (%)	53 (15·6)	56 (23·0)	36 (9·4)	**0·031**	1·61 [1·06–2·44]	**<0·001**	0·36 [0·22–0·58]	**0·001**	0·48 [0·32–0·73]
Occlusion (%)	57 (16·8)	107 (43·9)	159 (41·6)	**<0·001**	3·86 [2·64–5·65]	0·24	0·82 [0·59–1·14]	**0·003**	1·54 [1·16–2·04]
ICAD vs. VAD (%)	285 (74·0)	174 (58·4)	247 (55·6)	**<0·001**	1·85 [1·31–2·61]	0·55	1·11 [0·79–1·57]	**0·003**	1·54 [1·16–2·04]
Putative risk factors									
Hypertension (%)	94 (28·0)	51 (21·0)	99 (26·3)	0·065	0·68 [0·46–1·01]	0·086	1·42 [0·95–2·13]	0·56	1·10 [0·80–1·50]
Hypercholesterolemia (%)	67 (20·1)	41 (17·0)	69 (18·5)	0·39	0·81 [0·53–1·25]	0·55	1·13 [0·74–1·77]	0·98	1·00 [0·71–1·43]
Body mass index	24·4 ± 4·1	24·2 ± 3·7	24·6 ± 4·0	0·47	0·068	0·087			
History of migraine (%)	134 (40·2)	103 (42·4)	118 (31·2)	0·61	1·09 [0·78–1·53]	**0·003**	0·60 [0·42–0·84]	**0·001**	0·62 [0·47–0·83]
Preceding mild trauma (%)	154 (46·5)	97 (40·4)	135 (35·8)	0·17	0·78 [0·56–1·09]	0·24	0·82 [0·58–1·15]	**0·009**	0·69 [0·53–0·91]
Preceding infection (%)	74 (22·3)	38 (16·0)	72 (19·3)	0·069	0·66 [0·43–1·02]	0·49	1·17 [0·75–1·81]	0·79	0·95 [0·68–1·34]
Smoking (%)	166 (49·0)	116 (47·7)	208 (55·3)	0·74	0·94 [0·67–1·30]	0·087	1·34 [0·96–1·86]	0·092	1·26 [0·96–1·65]

Significant test results (*P*-values < 0.05) are printed in boldface.

*Delay (median, interquartile range) = number of days between onset of symptoms (ischemic or nonischemic) and admission at the hospital. **P*-values and odds ratios adjusted for delay onset admission. For comparison of delay between groups, we used the Mann–Whitney test. CeAD, cervical artery dissection; CI, confidence interval; ICAD, internal carotid artery dissection; OR, odds ratio; TIA, transient ischemic attack; VAD, vertebral artery dissection.

Table 2 Determinants of delayed stroke, analyzed in patients with ICAD or VAD separately

	Patients with ICAD				Patients with VAD			
	No stroke (n = 244)	Delayed stroke (n = 142)	P	OR [95% CI]	No stroke (n = 75)	Delayed stroke (n = 91)	P	OR [95% CI]
Age	46·2 ± 9·5	44·9 ± 9·1	0·210		39·4 ± 9·0	40·3 ± 10·8	0·563	
Male gender (%)	149 (61·1)	80 (56·3)	0·391	0·82 [0·54–1·25]	29 (38·7)	43 (47·3)	0·276	1·42 [0·76–2·64]
Presenting symptoms								
LS (%)	152 (62·3)	29 (20·4)	**<0·001**	0·16 [0·10–0·25]	n.a.			
Pain (%)	206 (84·4)	130 (91·5)	0·058	2·00 [1·01–3·96]	68 (90·7)	86 (94·5)	0·380	1·77 [0·54–5·83]
TIA (%)	69 (28·0)	19 (14·3)	**0·001**	0·39 [0·22–0·68]	43 (57·3)	8 (8·8)	**<0·001**	0·07 [0·03–0·17]
Vascular pathology								
Multiple (%)	23 (9·4)	20 (14·1)	0·179	1·59 [0·84–3·01]	10 (31·6)	25 (35·3)	**0·035**	2·46 [1·10–5·53]
Occlusion (%)	38 (15·6)	67 (47·2)	**<0·001**	4·84 [3·00–7·81]	14 (18·7)	32 (35·2)	**0·023**	2·36 [1·15–4·87]

Patients with multiple dissections affecting both carotid and vertebral arteries were excluded from these analyses.
CI, confidence interval; ICAD, internal carotid artery dissection; LS, local sign; n.a., not applicable; OR, odds ratio; TIA, transient ischemic attack; VAD, vertebral artery dissection.
Significant test results (*P*-values < 0.05) are printed in boldface.

Cervical artery dissection patients with delayed and immediate stroke showed a few significant differences. The low prevalence of multiple CeAD in patients with immediate stroke may be related to the short delay between onset of CeAD and diagnosis as polyarterial clustered recurrence of CeAD is common during the first weeks (9). The longer delay between onset of CeAD and vascular imaging may explain the higher rate of multiple dissections in patients with delayed stroke. The low prevalence of pain and of migraine in patients with immediate stroke remains unexplained, but the findings may be biased by underreporting due to aphasia (10).

This cross-sectional study showed for the first time that patients with multiple CeAD and with VAD have an increased risk for delayed stroke. It confirms that occlusive ICAD increases the risk for stroke and demonstrated that the same is true for occlusive VAD. No further predictors for delayed stroke were identified. Our findings confirm that acute CeAD with mild, transient, or absent clinical symptoms may cause delayed stroke and is therefore considered as an emergency. Immediate stroke prevention of CeAD patients without ischemic stroke is necessary. As delayed stroke in CeAD patients can be predicted from early imaging findings, immediate cervical imaging is warranted also in those without primary signs of stroke.

Acknowledgements

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Supporting Information

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

Appendix: Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) investigators.