Adult cervicocerebral artery dissection: a single-center study of 301 Finnish patients

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Background and purpose: There are only few small studies assessing potential risk factors, comorbidity, and prognostic factors in adult spontaneous cervicocerebral artery dissection (CAD). Methods: We conducted a retrospective, hospital-based analysis on the prognostic factors and association of CAD with vascular risk factors in 301 consecutive Finnish patients, diagnosed from 1994 to 2007. Results: Two thirds of the patients were men (68%). Women were younger than men. Migraine (36% of all patients), especially with visual aura (63% of all migraineurs), and smoking were more common in patients with CAD compared with the general Finnish population. At 3 months, 247 (83%) patients reached a favorable outcome. Occlusion of the dissected artery, internal carotid artery dissection (ICAD), and recent infection in infarction patients were associated with a poorer outcome. ICAD patients had less often brain infarction, but the strokes they had were more severe. Seven (2.3%) patients died during the follow-up (mean 4.0 years, 1186 patient years). Six (2%) patients had verified CAD recurrence. Conclusions: This study provides evidence for the association of CAD with male sex, and possible association with smoking and migraine. Occlusion of the dissected artery, ICAD, and infection appear to be associated with poorer outcome.

Introduction

Spontaneous cervicocerebral artery dissection (CAD) is a common etiology of ischaemic stroke in young adults [1]. The pathophysiology and risk factors of CAD are incompletely understood [2]. CAD is probably a multi-factorial disease with a genetic predisposition which may cause arterial wall weakness [3,4] and dysfunction [5]. Dissections often are triggered by environmental factors such as minor hyperextension-rotation trauma [6]. Peaking frequency at age 40–50 years was reported [7–9]. Inconsistent data exist about the gender differences in CAD [9–11]. Chiropractic manipulation, recent respiratory tract infection, and migraine were suggested to be risk factors in non-population-based studies [6]. A history of hypertension was associated with an increased risk of CAD [12], but none of the other conventional vascular risk factors for stroke. In most studies, recurrence rate of CAD was low [13,14]. Ischaemic stroke and arterial occlusion were the only independent factors associated with poor outcome [8]. In a recent study, 70% of patients achieved excellent recovery, i.e. modified Rankin Scale (mRS) 0–1 at 6 months, and the mortality rate was 1% [8]. Our study assesses the predictors of outcome and the debated association of CAD with common vascular risk factors including migraine in 301 CAD patients. We also analyzed gender differences, outcome, and recurrences, about which limited data exist.

Methods

This study was approved by the Ethics Committee for Gynecology and Obstetrics, Otology and Ophthalmology, Neurology and Neurosurgery of the University Central Hospital of Helsinki (statement 8.2.2007, 182/E9/06), and the research permit was granted by the Clinic of Neurology of the same hospital (14 September, 2006). Our hospital serves as the only neurological emergency unit and a teaching hospital for a defined population of 1.5 million. In our region, practically all CAD patients are diagnosed in the neurological units of...
our hospital. Potential candidates were identified using electronic search of the hospital’s databases for diagnoses related to CAD and stroke, and their medical records were reviewed by stroke neurologists. Radiological images of patients in whom CAD was considered possible were re-analyzed by an experienced neuroradiologist (O.S.). In case of uncertainty, patient was excluded. All patients included in the study had one or more of the typical diagnostic radiological findings presented in Table 1. For diagnosing intramural hematoma in CT-angiography, the following criteria were used: The diameter of the artery was greater than in the contralateral side and proximally/distally to the dissection, and the residual lumen was eccentric in location relative to the surrounding hematoma. Patients presenting with subarachnoid hemorrhage (SAH) were treated in a neurosurgical unit and were not included in the present study [15]. There were 233 patients included in the study who were re-interviewed to complete the lacking data.

Our register consists of all verified CAD patients treated at our neurological department at the Meilahti Hospital between January 1994 and August 2007, and all patients diagnosed at the two other neurological departments of our hospital (Jorvi and Peijas Hospitals) between January 2000 and August 2007. There is an overlap of intracranial CAD patients between the present and our previous study [15]. Altogether we excluded 133 patients for the following reasons: lived outside the catchment area; was treated as CAD, but the radiological diagnosis could not be verified; CAD occurred in other than internal carotid or vertebrobasilar arteries. An internal carotid artery dissection (ICAD) or vertebral artery dissection (VAD) located completely within the intracranial space was classified as intracranial dissection, and a dissection starting extracranially but extending intracranially as combined dissection. Recanalization of a stenosis was defined as radiologically normalized artery, and recanalization of an occlusion as reperfusion. Radiological follow-up varied from approximately 3–6 months. Follow-up information extended until the end of August 2008.

Risk factors for CAD and ischaemic stroke were defined as follows: A history of antihypertensive, antidiyslipidemic or antidiabetic treatment or blood pressure >140/90 mmHg, total cholesterol value >5.0 mmol/l, LDL >3, HDL < 1 or triglycerides >2 without treatment or fasting blood glucose ≥7 mmol/l during hospital stay. Infection was defined as a history of respiratory or gastrointestinal tract infection within 1 month before admission. The other evaluated vascu-

Table 1 Patient characteristics and radiological findings

<table>
<thead>
<tr>
<th></th>
<th>ICAD</th>
<th>VAD</th>
<th>ED</th>
<th>ID&amp;CD</th>
<th>Other</th>
<th>Uniarterial</th>
<th>Multiple</th>
<th>All non-SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>157 (52)</td>
<td>144 (48)</td>
<td>139 (46)</td>
<td>95 (32)</td>
<td>67 (22)</td>
<td>280 (93)</td>
<td>21 (7)</td>
<td>301</td>
</tr>
<tr>
<td>Age, mean</td>
<td>47.3</td>
<td>45.8</td>
<td>46.0</td>
<td>45.9</td>
<td>48.5</td>
<td>46.5</td>
<td>47.9</td>
<td>46.6</td>
</tr>
<tr>
<td>Women/Men (%)</td>
<td>43/114</td>
<td>54/90</td>
<td>46/93</td>
<td>33/62</td>
<td>18/49</td>
<td>89/191</td>
<td>8/13</td>
<td>97/204</td>
</tr>
<tr>
<td>Brain infarction (%)</td>
<td>99 (63)</td>
<td>122 (85)</td>
<td>87 (63)</td>
<td>74 (78)</td>
<td>60 (90)</td>
<td>208 (74)</td>
<td>13 (62)</td>
<td>221 (73)</td>
</tr>
<tr>
<td>Median NIHSS on admission If infarction mRS 0–2 at 3 months (%)</td>
<td>7</td>
<td>2</td>
<td>2.5</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>If infarction mRS 0–1 at 3 months (%)</td>
<td>114/153 (75)</td>
<td>133/144 (92)</td>
<td>120/137 (88)</td>
<td>77/95 (81)</td>
<td>50/65 (77)</td>
<td>228/276 (83)</td>
<td>19/21 (91)</td>
<td>247/297 (83)</td>
</tr>
<tr>
<td>Radiological findings, n (%)</td>
<td>85/153 (56)</td>
<td>103/144 (72)</td>
<td>96/137 (70)</td>
<td>59/95 (62)</td>
<td>33/65 (51)</td>
<td>174/276 (63)</td>
<td>14/21 (67)</td>
<td>188/297 (63)</td>
</tr>
<tr>
<td>Intramural hematoma</td>
<td>75 (48)</td>
<td>68 (47)</td>
<td>82 (59)</td>
<td>40 (42)</td>
<td>21 (31)</td>
<td>129 (46)</td>
<td>14 (68)</td>
<td>143 (48)</td>
</tr>
<tr>
<td>Intimal flap or double lumen</td>
<td>44 (28)</td>
<td>39 (27)</td>
<td>47 (34)</td>
<td>27 (28)</td>
<td>9 (13)</td>
<td>74 (26)</td>
<td>9 (43)</td>
<td>83 (28)</td>
</tr>
<tr>
<td>Dissecting aneurysm</td>
<td>18 (12)</td>
<td>8 (6)</td>
<td>22 (16)</td>
<td>4 (4)</td>
<td>0</td>
<td>16 (6)</td>
<td>10 (48)</td>
<td>26 (9)</td>
</tr>
<tr>
<td>Long filiform stenosis</td>
<td>55 (35)</td>
<td>66 (46)</td>
<td>63 (45)</td>
<td>45 (47)</td>
<td>13 (19)</td>
<td>106 (38)</td>
<td>15 (71)</td>
<td>121 (40)</td>
</tr>
<tr>
<td>Rat tail-shaped or flame-like occlusion</td>
<td>46 (29)</td>
<td>11 (8)</td>
<td>13 (9)</td>
<td>13 (14)</td>
<td>31 (46)</td>
<td>55 (20)</td>
<td>2 (10)</td>
<td>57 (19)</td>
</tr>
<tr>
<td>Recanalized occlusiona</td>
<td>22 (14)</td>
<td>13 (9)</td>
<td>10 (7)</td>
<td>14 (15)</td>
<td>11 (16)</td>
<td>35 (13)</td>
<td>0</td>
<td>35 (12)</td>
</tr>
<tr>
<td>Pathognomonc sign(s)b</td>
<td>108 (69)</td>
<td>93 (65)</td>
<td>108 (78)</td>
<td>61 (64)</td>
<td>32 (48)</td>
<td>184 (66)</td>
<td>17 (81)</td>
<td>201 (67)</td>
</tr>
</tbody>
</table>

ICAD, internal carotid artery dissection; VAD, vertebrobasilar artery dissection. ED, extracranial dissection; ID, intracranial dissection; CD, intracranially extending dissection i.e. ‘combined’ dissection. Other: due to occlusion it was uncertain whether the dissection extended intracranially. Uniarterial: dissection only on one artery. Multiple: more than one dissected arteries. non-SAH: patients presenting without subarachnoid hemorrhage. We have previously reported data for patients presenting with SAH [15]. NIHSS: National Institutes of Health Stroke Scale.

aOclusion (if in ICA, >20mm above cartoid bifurcation) that recanalized into a long filiform stenosis.

bPathognomonc sign (intramural hematoma/double lumen/intima flap/dissecting aneurysm) and/or more than one typical radiological signs.
lar risk factors were current smoking, according to interview or medical records, and migraine, using the criteria from the International Classification of Headache Disorders (ICHD-II) [16].

Either a non-contrast brain CT or a MRI scan negative for SAH, together with no clinical suspicion of acute SAH, were considered sufficient to exclude SAH. Several neurological scores including National Institutes of Health Stroke Scale (NIHSS) and mRS were recorded on admission, discharge, and at 3 months. A mRS 0–2 at 3 months was considered a favorable outcome, and mRS 0–1 an excellent outcome. Odds ratios were calculated using information about the prevalence of risk factors in the general Finnish population, obtained from Statistics Finland (http://www.stat.fi/index_en.html) and Finnish database for healthcare professionals (http://www.terveysportti.fi).

Immediately after the diagnosis was established and SAH was excluded, most patients received either intravenous full-dose heparin sulfate or subcutaneous low molecular weight heparin. In 95% of patients (286/301), oral warfarin was initiated within few days after diagnosis and continued for at least 3 months. Heparin was discontinued when warfarin treatment reached target plasma levels (international normalized ratio 2.0–3.0). Sixteen patients (5.3%) received intravenous thrombolysis, five of whom had an intracranial or combined dissection.

Statistical analyses

The normality of distributions was tested with one-sample Kolmogorov–Smirnov test. Parametric test (t-test) was used to test differences with respect to age, since age was, together with pack years of smoking and cigarettes smoked daily, the only normally distributed variable. Groupwise comparisons between non-parametric ordinal variables were made using the Mann–Whitney U-test and Kruskal–Wallis H-tests. Chi-square, Fisher’s exact, and Newcombe–Wilson tests were applied to univariate dichotomous variables. Stratified analysis was performed in all calculations where Chi-square test was statistically significant to exclude important potential confounders (e.g. presence vs. absence of infarction/gender/ICAD vs. VAD/intracranial vs. extracranial CAD). Logistic regression was used to test whether the results in chi-square and stratified analyses were true (factors associated with outcome, recanalization, and when comparing men and women). Predictors of clinical outcome were analyzed also separately for the subgroup of patients with stroke. A commercially available, statistical software package spss, version 14.0.1(SPSS Inc., Chicago, IL, USA) was used. A two-tailed value of \( P < 0.05 \) was considered statistically significant. If Bonferroni correction is used, a two-tailed value of \( P \leq 0.001 \) is statistically significant.

Results

Diagnostics and patients

Our hospital-based register consists of 301 consecutive patients with 322 CADs on admission (280, 93% unilateral; 21, 7% two-vessel), all presenting without SAH. The frequencies of different radiological findings, different ICAD and VAD subtypes, age and gender distribution of our patients, are displayed in the Table 1. Diagnostic magnetic resonance angiography (MRA) was done in 220 (73%), MRI in 217 (72%), digital subtraction angiography (DSA) in 22 (7%), CT-angiography in 91 (30%), and ultrasound examination in 125 (42%) patients. Follow-up imaging at 3 and/or 6 months using MRA was done in 183 (61%), DSA or CT-angiography in 83 (28%), and ultrasound examination in 57 (19%) patients. Eighteen patients (6%) did not undergo follow-up imaging. The mean age at onset was 46.6 years (range: 15–79, median 46). A clear male preponderance was observed (68%, \( P < 0.001 \)), and men were older than women (47.8 vs. 44.0, \( P = 0.006, 95\% CI: 1.1–6.3 \)).

Vascular risk factors

Lifetime migraine history was obtained for 271 (90%) patients by re-interviewing or based on medical records. There were 97 (36%) patients who had migraine (53%, 48/91 of women; 27%, 49/180 of men, \( P < 0.001 \)). Migraine subtype was obtained from 97% (94/97) of migraineurs, 63% (59/94) of which had migraine with aura (72%, 33/46 of women; 54%, 26/48 of men, \( P = 0.078 \)).

In our series, 39% (80/204) of men and 29% (28/97) of women were active smokers at the time of hospitalization. The number of cigarettes smoked daily could be verified for 79 (73%) smokers. The mean were 15.7 for men (median 18) and 12.9 for women (median 14). Mean number of pack years smoked was 13.8 years (median 10, range < 1 to 80). None of the other investigated vascular risk factors were enriched in our patients compared with the general population. Patients with hypertension and dyslipidemia were older than other patients (49.6 vs. 44.5, \( P < 0.001, CI: 2.7–7.6 \); 49.0 vs. 43.2, \( P < 0.001, CI: 3.4–8.2, \) respectively).

Outcome and its predictors

The outcomes at 3 months are depicted in Table 1. Follow-up information was obtained for 297 (99%)
patients. Mean follow-up time was 4.0 years (median 3.1, range: 0.1–13.2). Two patients died in hospital because of their brain infarctions. Five patients died after more than 3 months, of whom one had a new brain infarction, one died of lymphoma, and three of unknown causes. Anticoagulation treatment was stopped in one patient because of metrorrhagia. No other overt bleeding complications were observed. Six (2%) new CADs, verified by vascular imaging, were observed during the follow-up. Two of these were asymptomatic findings in a control imaging, and four were manifested by transient ischemic attack, Horner’s syndrome, headache, or neck pain. One had a new brain infarction. None of the recurrences occurred in the previously affected artery. In addition, there were five patients who had symptoms during the follow-up, without new CAD imaging findings. These included dissection of ascending aorta, one brain stem infarction in a VAD patient, and two transient ischemic attacks (TIA) in the territory of the previously dissected vessel. No other neurovascular events leading to hospitalization were observed during the 1186 patient years’ follow-up.

Higher NIHSS score on admission was associated with poor outcome (P < 0.001). Patients with ICAD had less often brain infarction (P < 0.001), but suffered from more severe strokes (Table 1, P < 0.001) compared with VAD patients, based on their higher NIHSS-score, and a poorer outcome (P < 0.001). Patients with occlusion of the dissected artery had more often brain infarctions (90% 119/133 vs. 61%, 102/168, P < 0.001), and therefore less often excellent outcome (55%, 72/131 vs. 70%, 116/166, P = 0.008). In the subgroup of patients with brain infarction, patients with recent infection less often achieved excellent outcome than those without infection (9/33, 27.3% vs. 103/185, 55.7%, P = 0.003). Stenoses recanalized more often than occlusions (73%, 114/156 vs. 31%, 39/127, P < 0.001). Patients in whom artery recanalization was observed, were younger (age 43.8 vs. 49.4, P < 0.001), and had returned to work more often by 3 months (59%, 80/135 vs. 43%, 42/97, P = 0.016), whereas measured by mRS, outcome versus recanalization did not reach statistical significance. Factors associated with lack of recanalization were smoking (P = 0.017) and older age (t-test, P < 0.001). Patients with dissecting aneurysms without SAH had less infarctions than others (P = 0.005), and thus a more favorable outcome (P = 0.019). Patients with extracranial CAD had less often infarctions (P < 0.001), but their outcome was not significantly better (Table 1). Other factors lacking correlation with outcome were age, gender, multiple versus uniarterial CAD, migraine anamnesis, hypertension, diabetes, smoking, and hypercholesterolemia.

Discussion
As far as we are aware of, our series is the largest single-center study published to date on CAD. Our results suggest the association of CAD with male sex, smoking, and migraine. Furthermore, occlusion of the dissected artery, ICAD, and infection appear to be associated with a poorer outcome. Our results are in agreement with the observation that women are younger than men at CAD onset [11,17]. In our patients, CAD was over twice as common amongst men [9–11], whereas the occurrence of multiple CADs were similar in both sexes. There are several genetic and environmental factors that could potentially contribute to these gender differences and need to be further studied.

Only one small epidemiologic study has been published about the frequency of VAD in adult Americans [18]. We found no significant difference in the occurrence rates of ICAD and VAD. Arauz et al. reported a series of 130 consecutive Mexican CAD patients of which 72 had VAD (55%) and 58 ICAD (45%) [19]. In the study by Lee and co-workers, 35% of their 48 patients were diagnosed by MRA and 13% by MRI [18]. It is likely that the differences in occurrence rates are at least partly because of differences in the diagnostic investigations and the applied criteria.

There are no epidemiological studies about the frequency of intracranial CADs. Our results suggest that nearly a third (32%) of all non-SAH CADs are either located or extend to the intracranial space. This number is comparable to that reported by Arnold et al. [20]. The lack of bony canal and looser connective tissue surrounding internal carotid artery in the cervical segment could explain why dissecting aneurysms were more common amongst ICAD than VAD patients.

However, dissecting aneurysms were also typically observed in patients with multiple CADs, supporting the idea suggested by histological studies of inherited and/or acquired connective tissue abnormalities with vascular phenotype in CAD patients [2–4]. Taking into account the considerable variation in the prognosis of patients with dissecting aneurysms [15], it is plausible to hypothesize that there are several predisposing vascular phenotypes.

Three small case–control studies have reported that migraine was more frequent amongst CAD patients [21–23]. This was later interpreted as a proof of migraine as an independent risk factor for CAD [24]. Taking into account the reported migraine prevalence numbers [25], migraine was slightly more common in our patients compared with the general population. There was a considerably high percentage of migraine with aura amongst the migraineurs. Accordingly, migraine with aura was associated with CAD giving
an odds ratio of 5.17 (CI: 2.62–10.19, with $P = 0.002$) for women, and 4.05 (CI: 2.10–7.80) for men. This comorbidity tallies with common predisposing genetic backgrounds for migraine with aura and CAD [26].

The average prevalence of adult (15–64 years) smokers in Finland from 1994 to 2006 was 27% for men (range: 26–30%) and 20% for women (18–20%) [27]. Smoking was thus associated with CAD giving odds ratio of 1.83 (CI: 1.26–2.65, with $P = 0.002$). Both the number of cigarettes smoked daily and the number of pack years were relatively high for both sexes. Previous studies demonstrated abnormal endothelial function [28] and increased oxidative stress [29] and proteolytic activity in the human arteries related to smoking. None of the other investigated vascular risk factors were enriched in our patients [12]. However, the association between arterial hypertension and CAD may depend, amongst other things, on the criteria of hypertension used [12].

Almost all of our patients received anticoagulation therapy, and 16 received intravenous thrombolysis. Our results are in line with studies reporting generally good outcomes and low recurrence rates for patients with non-SAH CADs [13,14]. The low number of bleeding complications tallies with our previous data on the safety of anticoagulation therapy in CAD [15]. In contrast to some of the prior studies, the outcome was quite similar for intracranial and extracranial CADs presenting without SAH [15]. A recent multi-center study reported as high recurrence rate as 15% during the course of a 1 year follow-up [30]. In our patients, the verified recurrence rate was 2%, of whom 3/6 were asymptomatic or were manifested as TIA or non-infarction symptoms, whilst only one new brain infarction was observed. The fact that none of the verified recurrences occurred in the initially affected arteries, further suggests the presence of structural arterial vessel wall fragility most likely secondary to a genetic abnormality.

Stroke and occlusion of the dissected artery on admission were previously reported as the only independent factors associated with poor outcomes in CAD [8]. We observed the same associations and a few more. As reported [31], the association between recanalization of the affected artery during follow-up and outcome measured by mRS did not reach statistical significance in the present study. However, those in whom recanalization occurred had returned to work more often by 3 months than those without recanalization. This is in keeping with the lower rate of brain infarctions associated with more often recanalizing initially stenosed arteries. Also non-SAH dissecting aneurysms were associated with favorable outcome, possibly because of non-occlusive tearing of the vessel wall closer to the adventitial layer. We reported that dissecting aneurysms presenting with SAH were associated with poor outcome [15]. The present data suggest further that anamnestic infection [32] and ICAD are associated with a poorer outcome. Typical of anterior circulation brain infarction, ICAD patients had more severe strokes and worse outcome compared with VAD patients.

The main limitation of the present study is the lack of a control group. Patients were included over a long period which makes the case–control design retrospectively difficult. Large patient series from many countries with diverse genetic backgrounds are needed to obtain the full clinical presentation of CADs, and to detect possible variations between different populations. Large scale multi-center genome studies such as the CADISP consortium (http://www.cadisp.org) will hopefully further elucidate pathophysiological mechanisms of this major cause of stroke in young people.

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Authors’ contributions

Manuscript drafting or manuscript revision for important intellectual content: all authors. Manuscript final version approval: all authors. Tiina M. Metso: study concept and planning, data acquisition, analysis, literature search, interpretation, and manuscript writing. Antti J. Metso: study concept and planning, data acquisition, analysis, literature search, interpretation, and manuscript writing. Oili Salonen: data collection, logistic and administrative support. Elena Haapaniemi: study concept and planning, and data acquisition. Jukka Putaala: data acquisition. Ville Artto: data acquisition. Johanna Helenius: data acquisition. Markku Kaste: study concept and planning, interpretation, and logistic and administrative support. Turgut Tatlisumak: study concept and planning, analysis, literature search, interpretation, manuscript writing, and logistic and administrative support.

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