Prognosis and Safety of Anticoagulation in Intracranial Artery Dissections in Adults

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Background and Purpose—To characterize different forms of intracranial artery dissections (IADs), and to test the assumption that IADs are frequently associated with subarachnoid hemorrhage (SAH) and poor outcome, and that anticoagulant therapy is contraindicated in these patients.

Methods—We studied 81 consecutive non-SAH IAD patients and 22 IAD patients with SAH, diagnosed between 1994 and 2004 and 1998 and 2004, respectively, and treated the former patients immediately with heparin, followed with at least 3 months of warfarin. Outcomes were recorded at 3 months.

Results—Approximately one-third of all cervicocephalic artery dissections were identifiably either completely located intracranially or extended into the intracranial space. At 3 months, 64 of the 81 non-SAH patients (79%) had a favorable outcome (modified Rankin Scale, 0 to 2); 1 patient died of brain infarction in the acute stage. Only 1 aneurysm developed during follow-up in the non-SAH group, and no intracranial bleeding was observed during anticoagulant treatment. Those presenting with SAH formed ≈25% of all IADs, and 21 cases out of 22 (95%) were associated with ruptured fusiform dissecting aneurysm. This latter group displayed significantly worse outcomes: 7 died, and only 7 had modified Rankin Scale 0 to 2 at 3 months.

Conclusions—Our results provide important information for clinical practice. IADs appear to polarize into 2 groups: (1) nonaneurysmatic IADs presenting without SAH that are associated with favorable outcomes and safe anticoagulant therapy; and (2) aneurysmatic IADs, characterized by SAH and poorer prognosis. Literature on IADs may have been biased toward group 2. (Stroke. 2007;38:1837-1842.)

Key Words: anticoagulants ■ cervical artery ■ dissection ■ prognosis ■ stroke
Clinical Features of Intracranial Dissections

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>ID* Carotid</th>
<th>Vertebrobasilar</th>
<th>All Non-SAH</th>
<th>SAH-Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years and range)</td>
<td>n=23</td>
<td>n=22</td>
<td>n=59</td>
<td>n=81</td>
</tr>
<tr>
<td>Women/Men (%)</td>
<td>8/15 (53.3%)</td>
<td>8/14 (57.1%)</td>
<td>26/55 (52%)</td>
<td>11/11 (50%)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (65.2%)</td>
<td>13 (59.1%)</td>
<td>31 (52.5%)</td>
<td>44 (54.3%)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>10 (43.5%)</td>
<td>7 (31.8%)</td>
<td>23 (39.0%)</td>
<td>30 (37.0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (43.5%)</td>
<td>2 (9.1%)</td>
<td>45 (76.3%)</td>
<td>46 (56.8%)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>14 (60.9%)</td>
<td>2 (9.1%)</td>
<td>48 (81.4%)</td>
<td>49 (60.5%)</td>
</tr>
<tr>
<td>Horner</td>
<td>9 (39.1%)</td>
<td>7 (31.8%)</td>
<td>15 (25.4%)</td>
<td>22 (27.2%)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>6 (26.1%)</td>
<td>2 (9.1%)</td>
<td>21 (35.6%)</td>
<td>23 (28.4%)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>6 (26.1%)</td>
<td>2 (9.1%)</td>
<td>21 (35.6%)</td>
<td>23 (28.4%)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>3 (13.0%)</td>
<td>1 (4.5%)</td>
<td>12 (20.3%)</td>
<td>13 (16.0%)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>3 (13.0%)</td>
<td>2 (9.1%)</td>
<td>7 (11.9%)</td>
<td>9 (11.1%)</td>
</tr>
<tr>
<td>Pulsatile tinnitus</td>
<td>2 (8.7%)</td>
<td>2 (9.1%)</td>
<td>5 (8.5%)</td>
<td>7 (8.6%)</td>
</tr>
<tr>
<td>Brain infarction</td>
<td>17 (73.9%)</td>
<td>15 (68.2%)</td>
<td>53 (89.8%)</td>
<td>68 (84.0%)</td>
</tr>
<tr>
<td>Decreased level of consciousness</td>
<td>3 (13.0%)</td>
<td>0</td>
<td>6 (10.2%)</td>
<td>6 (7.4%)</td>
</tr>
<tr>
<td>Number of Vessels</td>
<td>n=24</td>
<td>n=59</td>
<td>n=22</td>
<td>n=85</td>
</tr>
<tr>
<td>Intramural hematoma</td>
<td>3 (12.5%)</td>
<td>15 (25.4%)</td>
<td>4 (18.2%)</td>
<td>18 (21.2%)</td>
</tr>
<tr>
<td>Intima flap or double lumen</td>
<td>8 (33.3%)</td>
<td>12 (20.3%)</td>
<td>9 (40.9%)</td>
<td>11 (16.6%)</td>
</tr>
<tr>
<td>Long filiform stenosis</td>
<td>12 (50%)</td>
<td>31 (52.5%)</td>
<td>9 (40.9%)</td>
<td>35 (55.6%)</td>
</tr>
<tr>
<td>Recanalized occlusion†</td>
<td>1 (4.2%)</td>
<td>6 (10.2%)</td>
<td>1 (4.5%)</td>
<td>6 (9.5%)</td>
</tr>
<tr>
<td>Rat tail-shaped or flame-like occlusion</td>
<td>2 (8.3%)</td>
<td>7 (11.9%)</td>
<td>4 (18.2%)</td>
<td>6 (9.5%)</td>
</tr>
<tr>
<td>Pseudoaneurysm or dilatation</td>
<td>0</td>
<td>1 (1.7%)</td>
<td>1 (4.5%)</td>
<td>1 (1.2%)</td>
</tr>
</tbody>
</table>

1.4 million. Radiological images were analyzed by experienced neuroradiologists. All patients included in the study fulfilled the diagnostic criteria presented in Table.

Non-SAH Patients

All cases of diagnosed CCAD treated at the Department of Neurology between January 1994 and October 2004 were reviewed. Out of 256 patients with CCAD, 81 had IAD. A dissection located completely within the cranial cavity was classified as “combined dissection,” and a dissection starting extracranially but extending intracranially as “combined dissection.”

Several neurological scores including National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale, modified Rankin Scale (mRS), and Barthel Index were recorded on admission, discharge, and at 3 months. Radiological follow-up time varied from ~3 to 6 months. For those patients for whom the control imaging had been performed at 3 months and the dissected artery remained either occluded or stenosed, another vascular imaging was performed at ~3 to 6 months. For those patients for whom the control imaging had been performed at 3 months and the dissected artery remained either occluded or stenosed, another vascular imaging was performed at ~3 to 6 months. Follow-up imaging was considered sufficient to exclude SAH.

SAH Patients

In our center, all patients with SAH are treated at the Department of Neurosurgery. To avoid a bias, and to identify cases in which SAH was probably caused by an IAD, we reviewed all medical records and images of patients hospitalized between August 1998 and October 2004 with the diagnosis of SAH. Positive cases typically presented with a fusiform aneurysm, double lumen, and/or intramural hematoma or displayed fusiform aneurysm with arterial wall irregularity together with no notable arteriosclerosis.

Statistical Analysis

The normality of distributions was tested with Shapiro-Wilk test. Parametric test (t test) was used to test differences with respect to age as age was the only normally distributed variable. Groupwise comparison between 2 nonparametric class variable groups was made using the Mann-Whitney U test. The χ², Fisher exact, and Newcombe-Wilson hybrid score tests were applied to univariate
Results

Non-SAH Patients

Relative frequencies of different IADs, age and gender distribution, radiological findings, symptoms at onset, and data about brain infarctions are displayed in the Table. Of the 81 patients, 55 (67.9%) were men. Women were significantly younger than men (P=0.0060; 95% CI, 2.2 to 12.8). No other gender differences were observed. There were 23 patients with intracranial dissection and 57 patients with combined dissection. One patient had bilateral VAD: one was solely intracranial, the other combined. The number of diagnosed IADs increased constantly over time; 22 cases were found during 1994 to 1999 (3.7/year), and 59 cases later (12.2/year).

We identified 85 dissections: 22 (25.9%) in internal carotid artery (ICA), all unilateral, and 62 (72.9%) in VA (54 unilateral, 4 bilateral), and 1 (1.2%) in the basilar artery (male, age 54). VAD was associated with basilar artery occlusion in 8 patients, basilar artery stenosis or vessel wall irregularity in 6 patients, and occlusions in posterior inferior cerebellar artery (n=2), superior cerebellar artery (n=1), and posterior cerebral artery (n=1). One dissection occurred in the basilar artery only, and 1 patient with ICAD had vessel wall irregularity in the middle cerebral artery. Among intracranial dissections, there were 17 patients with VAD (1 bilateral; mean age, 42.9; range, 22 to 39 years), 5 with ICAD (mean age, 34.0; range, 21 to 56 years), and one with basilar artery dissection. Among combined dissections, there were 40 patients with VAD (2 bilateral; mean age, 47.4; range, 17 to 68 years) and 17 with ICAD (mean age, 42.8; range, 15 to 57 years). There were no differences between left- and right-side dissections in any aspect.

Diagnostic imaging studies in the acute phase included MRA in 76, MRI in 75, ultrasound examination in 31, digital subtraction angiography in 8, and CT angiography in 8 patients. Dissections were classified as either occlusive or stenotic. No aneurysms were detected in the acute stage. During the follow-up, one aneurysm was observed. At 3 and 6 months, MRA was performed in 32 and 48 patients, ultrasound examination in 6 and 1 patients, and CT angiography in 2 and 2 patients, respectively. The findings were classified as recanalization, partial recanalization of an initially occluded artery, and no change.

After diagnosis, patients received immediate anticoagulation treatment for 5 to 7 days with either intravenous heparin sulfate (n=37) and/or subcutaneous low-molecular-weight heparin (n=51), followed by oral warfarin (n=76) for at least 3 months. Eight patients received intravenous thrombolytic therapy (alteplase), mostly for acute basilar artery occlusion, and 4 patients had aspirin, together with low-molecular-weight heparin. Invasive therapeutic interventions were not used.

Infarctions occurred more often in patients with vertebro-basilar dissections (ICAD versus VAD, n=15 versus 53; P=0.018). Patients with clinical deterioration (n=22) were immediately re-evaluated clinically and underwent brain imaging. No cases of SAH were observed. Cardiovascular risk factors for IAD patients were not different from patients with extracranial artery dissection or from the general Finnish population.

Only one patient died (woman, age 45; infarction in the acute phase). On admission, median Glasgow Coma Scale was 15 (range, 3 to 15), and median NIHSS 3 (range 0 to 30). At 3 months, 63 patients (77.8%) had no disability (Barthel Index, 100), 64 patients (79.1%) had a favorable functional outcome (mRS, 0 to 2), and only 5 patients (6.2%) were still hospitalized. There was no statistically significant correlation between the site of dissection and 3-month outcome among patients with infarctions (median mRS, 1 for both ICA and VA territory infarcts; range, 0 to 3 and 0 to 6, respectively). Severity of stroke (NIHSS) on admission correlated well (P<0.0001) with the outcome (mRS) at 3 months. There was no difference in the outcome between intracranial dissections and combined dissections. The prognosis had no correlation with patient age. As expected, those with basilar artery thrombosis had significantly more severe infarctions on admission (median NIHSS, 18.5; range, 5 to 30) and poorer prognosis at 3 months (median Barthel Index, 65; range, 0 to 100; median mRS, 4.5; range, 2 to 6) compared with others (median NIHSS, 2; range, 0 to 24; median Barthel Index, 100; range, 10 to 100; and median mRS, 1; range, 0 to 5; P<0.0001 for all). No recurrences or new infarctions were detected clinically or radiologically during the 3-month follow-up. Despite the anticoagulant medication, clinical or imaging signs of SAH developed in none of our patients.

The number of stenosed and occluded arteries and changes in the status of the dissected arteries in the non-SAH patients are displayed in the Figure. Occlusions resulted in infarctions (n=34, 94.4%) more often than stenoses (n=34, 75.6%; P=0.0210). Yet, for the former, the outcome was not worse. Complete recanalization was observed in 31 of the 43 (72.1%) initially stenosed and in 7 of the 34 (20.6%) initially occluded arteries. Partial recanalization occurred in 10 (29.4%) of the initially occluded arteries. Recanalization was observed as often in ICADs and VADs and in women and men. Recanalization had no effect on outcome, and those with later recanalization had similar NIHSS scores on admission compared with those with no change.

SAH Patients

A fusiform aneurysm, caused by a dissection, was diagnosed in 21 of the 22 (95%) patients with SAH. In 7 patients a pathognomonic double lumen and/or intramural hematoma was observed, whereas in 15 patients a fusiform aneurysm and arterial wall irregularity together with no notable arteriosclerosis indicated dissection. Diagnosis was made by using digital subtraction angiography (n=11) or CT angiography (n=11); all patients had a brain CT revealing blood in subarachnoid space. The SAH rate would thus be 25% of IADs; as during the same 6-year period, 67 patients with IAD were treated in the Department of Neurology. None was disabled before SAH. Aneurysms were located mainly in VA (11 patients), but also in posterior inferior cerebellar artery
(3 patients), basilar artery (3 patients), anterior cerebral artery (2 patients), superior cerebellar artery, posterior cerebral artery, and pericallosal artery (1 in each). Aneurysm was operated on in 20 patients.

On admission, the neurological scores for SAH patients varied considerably (median Glasgow Coma Scale, 11.5; range, 3 to 15; median NIHSS, 12; range, 0 to 41 for the 19 patients for whom it was recordable). Three patients died soon after arrival in the hospital and 4 died later; the 3-month mortality rate was 31.8%. At 3 months, median mRS was 4 (range, 0 to 6), and median Glasgow Coma Scale for the survivors was 15 (range, 3 to 15), but only 7 patients (31.8%) achieved a favorable outcome. Compared with non-SAH patients, the condition of SAH patients on admission was significantly worse assessed by Glasgow Coma Scale (P<0.0001), and their outcome was significantly poorer according to mRS (P<0.0001).

Discussion

The present data indicate that approximately one-third of all CCADs are identifiably either completely located intracranially or extend into the intracranial space. Thus far, IADs have only been reported as numerous single case reports or a small series of patients or as reviews of large numbers of previous original reports. There are no comparable data available on the relative incidence of IAD versus extracranial artery dissections. This is, to our knowledge, the largest reported series of patients with IAD. Our patient population is representative from the following viewpoints. In our catchment area, our hospital is the only neurological and neurosurgical emergency unit of those who survived to hospital admission. Second, we included all consecutive patients both from neurological and neurosurgical units overcoming a potential inclusion bias. Yet CCAD may be revealed by isolated headache only, and there are patients who are likely to have CCAD, although their diagnosis cannot be verified radiologically. This patient population may distort data being either included or excluded. To allow firm conclusions, we included only patients who fulfilled the radiological criteria presented. Inherent to any retrospective study, possible underascertainment and miscoding of diagnoses of minimally symptomatic patients and patients with very uncommon symptoms could not be unambiguously excluded.

The present data suggest that an initial CT or MRI scan negative for SAH, together with no clinical suspicion of acute SAH, are sufficient to exclude SAH. It appears that IADs break into 2 subgroups with respect to clinical findings, safety of anticoagulation, and prognosis. Nonaneurysmatic IADs form approximately three-fourths of all IADs and seem to be associated with favorable outcomes and safe anticoagulant therapy, whereas aneurysmatic IADs that form approximately one-fourth of all IADs are characterized by SAH and poor prognosis. After the first event, no intracranial bleeding, CCAD recurrences, or new infarctions were detected clinically or radiologically during the 3-month follow-up. This is in agreement with data revealing retrospectively a recurrence rate of ≈0.9% among 457 CCAD survivors during at least 1 year of follow-up. In that study, the recurrences were transient ischemic attacks and strokes, and no SAHs were observed.

Both aneurysmatic and nonaneurysmatic forms of IADs, alike cerebral infarctions, occurred predominantly in the vertebrobasilar system. Including bilateral dissections as 2 CCADs, SAH was observed in ≈15% of anterior circulation IADs and in ≈24% of vertebrobasilar system IADs. Unlike the internal carotid artery, which enters the skull through a narrow osseous foramen, VA enters the skull through the foramen magnum, which may explain why many VADs...
extend or occur intracranially.\textsuperscript{19} Interestingly, among children with IAD, anterior circulation was more commonly involved;\textsuperscript{20} among adults, patients with ICAD were younger than those with VAD.\textsuperscript{16} We observed the same difference, but it was statistically insignificant. In keeping with the literature, most of our patients were males, and men were older than women.\textsuperscript{5,16} Those with intracranial dissection were younger than extracranial dissection patients,\textsuperscript{16} both for VADs and ICADs, but for the former the difference was statistically insignificant. Arterial occlusions resulted in infarction more often than stenoses. Complete or partial recanalization occurred in half (17 out of 34) of initially occluded arteries, and complete recanalization in three-fourths (31 out of 43) of initially stenosed arteries, with these figure being somewhat lower than those reported for extracranial dissection patients (62\% and 90\%, respectively) by Sturzenegger et al.\textsuperscript{21} No specific risk or predisposing factors that would differentiate patients with IAD from those with extracranial artery dissections or from the Finnish population in general\textsuperscript{22} were observed.

It has been proposed that IADs share a poorer prognosis than extracranial artery dissections and that IADs are frequently associated with death and disability.\textsuperscript{7,14} Accordingly, Bassetti et al\textsuperscript{16} reviewed all published cases of intracranial ICADs (n=59) years 1915 to 1993 and found a SAH rate of 20\%, fatal outcome in 72\% of all cases, and permanent neurological sequel in half of the survivors. The frequency and possible association of aneurysms with SAH and poor prognosis were not reported. Fullerton et al\textsuperscript{20} identified 79 studies published in MEDLINE in English between 1966 to 2000 that reported 118 CCAD patients younger than 18 years with a clear male dominance. Sixty percent of anterior cerebral circulation dissections and 21\% of posterior circulation dissections were intracranial. One-fourth of the patients died, and one-third of the survivors had neurological deficits.\textsuperscript{20} Interestingly, only 2 cases of SAH were observed. One was associated with severe head trauma, and the other with posterior cerebral artery dissecting aneurysm. Kitanaka et al\textsuperscript{24} reported 24 Japanese patients with intracranial VAD (16 with SAH). At least half of their patients either perished or remained severely disabled. Only 3 non-SAH patients had a favorable outcome. On admission, 14 of those with SAH displayed “pearl and string” signs and 2 had aneurysmal dilatation in the angiography, whereas in the non-SAH group, the corresponding numbers were 3 and 1, respectively.

Yoshimoto et al\textsuperscript{25} reported 10 patients (8 men) with basilar artery dissection of whom 4 presented with SAH, a fusiform aneurysm, and mainly poor outcome. For the non-SAH patients, the outcome was poor in 6 and moderate or good in 3 patients. Only 1 non-SAH patient had an unruptured fusiform dilatation attributable to dissection. Among our non-SAH patients, no unruptured aneurysms were observed on admission, and only 1 secondary aneurysm developed during follow-up. Ohkuma et al\textsuperscript{26} reviewed 49 cases of dissecting aneurysms of intracranial circulation diagnosed 1995 to 1999. They reported a ratio of intracranial dissecting aneurysms to all intracranial aneurysms to be 19.1\%, with SAH occurring in 56\% of the cases together with mainly poor prognosis.

Overall mortality among our patients (n=103) was 7.8\%, and for the non-SAH patients (n=81) it was 1.2\% (1.6\% for VADs and 0\% for ICADs). The good outcome of non-SAH patients (at 3 months, 79\% had mRS 0 to 2) is in contrast with the high mortality and morbidity rates reported for this patient group. Yet similar results have been published in small series.\textsuperscript{27,28} The discrepancy in the outcomes of patients between some of the previous reports and the recent ones, including our study, probably represents a publication bias, because cases diagnosed at autopsy dominated the early literature. We assume that the increase in the annual rate of IADs in our area after 1999 is attributable to a higher index of suspicion, stemming from improved awareness among physicians and higher performance imaging equipment. Improvements in diagnostic imaging, supportive stroke care, and increasingly used thrombolytic and anticoagulant/antiplatelet therapy may have had a positive impact on outcome.

Present results are important for clinical practice. Still, firm conclusions on prognostics and treatment options of CCADs are not yet available. Most experts treat extracranial CCADs with anticoagulants, usually for 3 to 6 months. IAD has been considered a contraindication for anticoagulant treatment, because it is thought to be associated with a high risk of SAH. In extracranial dissection, cerebral ischemia is generally presumed to be caused by embolism. In IADs, cerebral ischemia was suggested to be of hemodynamic origin and, because of increased risk of additional intramural bleeding, not amenable to anticoagulation.\textsuperscript{29} However, emboli in cerebral arteries were demonstrated in patients with IADs,\textsuperscript{30} favoring the use of anticoagulation, or at least indicating a randomized and controlled clinical trial to find out whether anticoagulant treatment can ameliorate outcome.

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Disclosures
None.

References


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