CME Risk of stroke and recurrent dissection after a cervical artery dissection

A multicenter study

E. Touzé, MD; J.-Y. Gauvrit, MD; T. Moulin, MD; J.-F. Meder, MD, PhD; S. Bracard, MD; J.-L. Mas, MD; for the Multicenter Survey on Natural History of Cervical Artery Dissection*

Abstract—*Objective:* To assess the risk of stroke, TIA, or dissection recurrence after a first event of cervical artery dissection (CAD). *Methods:* The authors undertook a historical cohort study of consecutive patients with a first event of CAD who were admitted in 24 departments of neurology within a period of at least 1 year. Patients were retrospectively selected from a stroke data bank or from the local administrative data bank using the 10th revision of the International Statistical Classification of Diseases. A neurologist and a radiologist reviewed all charts to validate diagnosis and collect data. In 2002, patients were interviewed by phone or during a visit by the local investigators. *Results:* Four hundred fifty-nine patients (mean age 44.0 ± 9.7 years) were included in the study. Among the 457 survivors, 25 (5.5%) could not be contacted in 2002 because they had moved. After a mean follow-up of 31 months, four (0.9%) patients presented a recurrent ischemic stroke attributable to either not yet completely recovered initial CAD (n = 2) or a recurrent CAD (n = 2). Eight (1.8%) patients had a TIA without CAD recurrence. Two TIA occurred at the acute stage of CAD. Of the six remaining TIA, only one was associated with chronic arterial stenosis. In addition, two patients had recurrent CAD without stroke, giving a total of four (0.9%) CAD recurrences. *Conclusions:* Patients with a first event of CAD have a very low risk of ischemic events or dissection recurrences. Ischemic events seem rarely to be in relation with chronic arterial lesions.

NEUROLOGY 2003;61:1347–1351

Cervical artery dissection (CAD) is one of the most frequent causes of ischemic strokes in young subjects.[1,2] Apart from neurologic damage due to initial stroke, the long-term prognosis of patients with CAD is commonly considered as good. However, studies devoted to the prognosis of patients with CAD are very scarce.[2,3] These studies were commonly conducted in single centers with relatively small samples of patients and were sometimes limited to an anatomic subtype of CAD.[4-10] The aim of our study was to assess the incidence of stroke, TIA, and symptomatic CAD recurrence in a large population of patients with a first event of CAD.

Methods. *Selection of patients.* In 2002, we undertook a historical cohort study of consecutive patients who presented with a first event of CAD and who were admitted in 24 French departments of neurology. Each participating center was asked to define a period of at least 1 year in which consecutive patients could be confidently identified from a stroke data bank or from the local administrative data bank using code for dissection (I670) of the 10th revision of the International Statistical Classification of Diseases (ICD).[11] Depending on the center, the starting date of the study ranged from January 1995 to January 2001. Only patients who were still alive 1 month after CAD were included. In each center, a neurologist and a neuroradiologist reviewed all charts to collect information on clinical presentation, vascular risk factors, history of trauma, and vascular imaging. We could not determine any reliable information on family history of dissection in the medical charts. CAD was classified as spontaneous or traumatic according to the judgment of investigators.[12] Diagnosis of CAD was made on the basis of ultrasound studies and MR angiography (MRA) or digital subtraction angiography (DSA) and was based on classic angiographic signs, namely, irregular stenosis ("string sign"), double lumen, and intimal flaps.[13,14] Occlusive forms had to be confirmed by the presence of a mural hematoma on cervical MRI, CT scan, or duplex sonography. Patients with artery occlusion without visible hematoma but with fibromuscular dysplasia or with an aneurysm on at least one other cervical artery were also considered as having a CAD.

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*See the Appendix on page 1350 for a list of Group members.

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Supported by the Société Française de Neurologie Vasculaire and the Société Française de Neuroradiologie.

Received June 13, 2003. Accepted in final form July 29, 2003.

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Table 1 *Baseline characteristics and factors associated with recurrent ischemic event in univariate analysis*

Features	All patients, n = 459	Recurrent ischemic event, n = 12	Univariate hazard ratio (95% CI)
Age ± SD, y	44.0 ± 9.7	43.0	1.0 (0.9–1.1)
Men, n (%)	243 (52.9)	4 (33.3)	0.4 (0.1–1.4)
Hypertension, n (%)	94 (20.5)	3 (25.0)	1.3 (0.3–4.7)
Minor trauma, n (%)	78/404 (19.3)	1 (8.3)	0.4 (0.1–3.1)
Severe trauma, n (%)	30/404 (7.4)	1 (8.3)	0.9 (0.1–7.0)
Migraine, n (%)	118 (25.8)	2 (16.7)	0.6 (0.1–2.9)
Smoking, n (%)	133 (29.0)	6 (50.0)	2.6 (0.8–8.0)
Fibromuscular dysplasia, n (%)	40 (8.7)	0	—
Multiple dissection, n (%)	72 (15.7)	5 (41.7)	3.5 (1.1–11.0)
Isolated local signs,* n (%)	107 (23.3)	2 (16.7)	0.6 (1.3–2.7)
No antithrombotic therapy at last visit or at recurrent event, n (%)	97 (22.4)	3/11 (27.3)	1.0 (0.3–3.6)

* Headache, neck pain, Horner syndrome, pulsatile tinnitus, or cranial nerve palsy located on the side of internal carotid artery dissection.

Follow-up. Most patients had been regularly monitored by their attending neurologist. In 2002, patients were interviewed by phone or during a visit by local investigators to check on recurrent events including stroke, TIA, or symptomatic recurrent dissection that might have occurred since their last visit and use of antithrombotic treatments. For patients who could not be contacted, the date of the last visit notified in the chart was used for the follow-up. The study coordinators validated all events after having reviewed medical charts. Stroke was defined by the acute occurrence of local neurologic signs lasting >24 hours in a location different from that of the previous stroke or worsening of an existing deficit lasting >1 week or >24 hours if accompanied by a new lesion on neuroimaging. We used American Heart Association criteria for the diagnosis of TIA.[15] Recurrent cervical artery dissection was defined in the same manner as for initial diagnosis. In patients with recurrent event, chronic arterial lesion was defined as a lesion (occlusion, stenosis, or aneurysm) persisting >6 months after the initial diagnosis of CAD.

Statistics. Categorical variables were compared with Pearson's χ^2 test and, when necessary, Fisher's two-tailed test. Continuous variables were compared with two-tailed *t*-tests for comparison of means. Kaplan–Meier analysis was used to assess the absolute risk of recurrent ischemic events. The predictive value of potential risk factors for recurrent ischemic events, including sex, age, hypertension, migraine, smoking, initial clinical presentation (isolated local signs vs stroke or TIA), trauma before CAD, multiple dissection, fibromuscular dysplasia, and use of antithrombotic treatment, was assessed with Cox proportional hazard models.[16] All tests were two tailed.

Results. The study population consisted of 459 patients. The majority of them (n = 318; 69.3%) were selected from a stroke data bank. The main characteristics of the population are shown in table 1. Initial clinical presentation was an ischemic stroke in 293 patients (63.8%), isolated local signs in 107 (23.3%), TIA in 54 (11.8%), and subarachnoid hemorrhage in 5 (1.1%). Among the patients with ischemic stroke, 16 of 293 (5.5%) had had at least one TIA within the month before their admission (mean delay 4.9 days, range 1 to 20 days). At diagnosis, 447 patients (97.4%) had had duplex sonography, 272 (59.3%) time-of-flight or gadolinium-enhanced MRA, 228 (49.7%) DSA, 244 (53.2%) cervical MRI with axial sections, and 12 (2.6%) CT scan. Seventy-two patients (15.7%) had multiple dissections. Overall, there were 384 carotid artery and 170 vertebral artery dissections, which corresponded to 367 stenotic, 115 occlusive, and 72 aneurysmal forms. Three patients had documented Marfan syndrome, and 40 (8.7%) were classified as having fibromuscular dysplasia by local investigators. Initial treatments consisted of hypocoagulant doses of heparin in 405 patients (88.8%), oral anticoagulants in 11 (2.4%), aspirin in 24 (5.3%), and recombinant tissue plasminogen activator in 2 (0.4%); 14 (3.1%) did not receive any antithrombotic treatment, and data were unavailable for 3 patients.

During the study period, two patients died before the date of the interview, 2.4 and 23.7 months after the initial CAD, one from suicide and the other from sudden unexplained death. Among the 457 survivors, 25 (5.5%) could not be contacted at the time of the interview because they had moved. These patients did not significantly differ from those who could be contacted as regards age, sex, risk factors, clinical presentation, or angiographic form of CAD. With use of the date of the last visit notified in the chart, the mean follow-up of patients who could not be contacted was 12.0 ± 13.4 months. Overall, the mean follow-up of our cohort was 31.0 ± 19.1 months (range 0.4 to 93.1 months). Among the 432 patients contacted in 2002, 97 (22.2%) did not receive any antithrombotic therapy, 304 (70.4%) received antiplatelet therapy (mainly aspirin), 23 (5.3%) oral anticoagulants, 1 an association of oral anticoagulant and aspirin, and treatment was unknown for 7 patients at the last visit. Patients who were not taking antithrombotic therapy at the last visit were younger (41.2 ± 11.6 vs 44.8 ± 9.0 years; $p = 0.001$), had severe trauma before dissection more often (13.8 vs 4.9%; $p = 0.02$), and had been followed longer (36.4 ± 19.4 vs 30.9 ± 19.1 months; $p = 0.01$) than those who were taking antithrombotic therapy at the last visit. Risk factors, initial clinical presentation, angiographic form of CAD, and number of dissected vessels did not significantly differ between patients with and without antithrombotic treatment at the last visit.

During follow-up, four patients (0.9%; 95% CI 0.02 to 1.7%) had an ischemic stroke (table 2), giving an incidence

Table 2 *Description of patients with recurrent events*

No.	Sex/age, y	Risk factors	Site of initial lesions	Initial anatomic lesions	Initial symptoms	Delay 1st–2nd event, mo	Type of 2nd event	Site of 2nd event	Antithrombotic therapy at time of 2nd event	Type of arterial examination performed at time of 2nd event	Evolution of initial lesions at time of 2nd event
						Stroke not due to recurrent CAD					
1	M/42.2	Hypertension, hypercholesterolemia	L ICA	St	TIA	4.9	IS	L ICA	None	DSA	L ICA An
2	F/44.8	0	L VA L ICA R ICA	Oc, St, An	IS	0.6	IS	L ICA	Oral anti-coagulant	MRA	Worsening of L ICA stenosis
						Stroke due to recurrent CAD					
3	F/44.7	Tobacco	R ICA	Oc	TIA, LS	38.8	CAD, IS	L ICA	Aspirin	Ultrasound, MRA	Resolution
4	F/38.5	Tobacco	L ICA	St	IS	34.2	CAD, IS	R ICA	ND	DSA	Persistence of R ICA occlusion
						Recurrent CAD without stroke					
5	M/40.6	Minor trauma	L ICA	St, An	LS	17.1	CAD, LS	L VA, R VA	ND	Ultrasound, DSA	Resolution
6	F/35.4	Migraine, minor trauma	R VA (V3)	St	IS	12.5	CAD, LS	R VA (V3)	ND	Ultrasound, MRA	Resolution
						TIA not due to recurrent CAD					
7	M/47.6	0	L ICA	St	IS, LS	4.0	TIA	L ICA	Aspirin	DSA	Occlusion of L ICA
8	M/41.3	Tobacco	R VA	St	IS, LS	2.4	TIA	R VA	Oral anti-coagulant	CT scan	Unknown at event, resolution at 4 mo
9	F/43.6	Migraine, hypercholesterolemia	R ICA	St	TIA	18.5	TIA	R ICA	Aspirin	Ultrasound	Resolution
10	F/40.4	0	R VA L ICA	St	LS	43.5	TIA	Undetermined	Aspirin	MRA	Resolution
11	M/54.4	Hypertension, tobacco, minor trauma	R ICA L ICA	St	LS	26.6	TIA	R ICA	Aspirin	DSA	Persistence of R ICA stenosis
12	M/47.3	Tobacco, severe trauma	R ICA	St, An	IS	12.0	TIA	R ICA	Aspirin	Ultrasound	Resolution
13	F/25.3	Hypertension, tobacco, migraine	L ICA	St	IS, LS	12.6	TIA	Undetermined	None	MRA, ultrasound	Resolution
14	F/46.2	Hypercholesterolemia	R VA L VA	St	LS, SH	51.9	TIA	Undetermined	None	Ultrasound	Resolution

CAD = cervical artery dissection; ICA = internal carotid artery; St = stenosis; TIA = transient ischemic attack; IS = ischemic stroke; DSA = digital subtraction angiography; An = aneurysm; VA = vertebral artery; Oc = occlusion; MRA = MR angiography; LS = local signs; SH = subarachnoid hemorrhage.

of 0.3%/year. Two of them occurred <6 months (0.6 and 4.9 months) after the initial event, in patients with not yet completely recovered initial dissection. The first patient had a carotid aneurysm and did not receive any antithrombotic treatment at the time of the recurrent event. In the second patient, a worsening of the left carotid artery stenosis was observed at the time of the stroke, which occurred despite a well-conducted anticoagulant treatment. The two other strokes were due to a contralateral recurrent carotid artery dissection that occurred 34.2 and 38.8 months after the first one. Eight patients (1.8%; 95% CI 0.5 to 2.9%) had a TIA without CAD recurrence, giving an incidence of TIA of 0.6%/year. Two TIA occurred in the territory of the initial dissection <6 months (2.4 and 4.0 months) after the initial event in patients with not yet completely recovered initial dissection. Of the six TIA that occurred >6 months after the initial dissection, three were in the territory of the initial CAD and three were in an undetermined territory. One patient had chronic carotid stenosis, and TIA were of undetermined etiology in the five remaining pa-

tients (see table 2). In univariate analysis, only the presence of multiple dissections at the initial presentation was significantly associated with an increased risk of ischemic event (see table 1). Multivariate analyses showed the same results, and adjusted hazard ratio for multiple dissections was 4.2 (95% CI 1.2 to 14.4). Exclusion of patients with severe trauma did not change the results.

Two patients had CAD recurrences with isolated local signs (see table 2). Therefore, a total of four CAD recurrences was observed in our cohort, giving an incidence of recurrent dissection of 0.3%/year. No dissection in other arterial territories was reported. No risk factor for CAD recurrence could be identified.

Discussion. This study is the largest one devoted to the incidence of cerebral ischemic events after a first event of CAD. As many centers participated in the study, referral biases are attenuated. Because of its retrospective design, our study is subject to potential criticisms regarding identification of cases of CAD and recurrent events. Cases of CAD were identified from stroke data banks or administrative databanks. In France, almost 100% of hospital stays lead to a medical summary coded with the 10th revision of the ICD. The most severe cases of CAD may have been missed because patients admitted in a critical neurologic state do not always have arterial examinations. Similarly, patients with isolated local signs are not always investigated and are likely to be underrepresented. Patients were regularly monitored by their attending neurologist, and no recurrent event that could have been missed in the medical chart was identified by the final interview. Therefore, significant events are not likely to have been missed. TIA are more difficult to diagnose because mild symptoms may not be pointed out by the patient and no objective confirmatory tests exist. Nevertheless, the diagnosis of TIA was confirmed by the attending neurologist and by the study coordinators in all cases.

The incidence of stroke (0.3%/year) and TIA (0.6%/year) in the current study is close to that reported in a series of 105 patients followed for 3 years, in which two patients (0.6%/year) had a recurrent stroke and three (1%/year) had a TIA.[6] In our study, 4 (2 strokes and 2 TIA) of the 12 ischemic events occurred within 6 months of acute CAD, when arterial lesions had not completely recovered, suggesting that the risk may be higher during this period.

The risk factors for recurrent events after CAD are not well known. The risk of ischemic events in patients with chronic aneurysmal,[17,18] occlusive, or severe stenotic forms[9,19] of CAD seems low. As our study was not designed to investigate the long-term evolution of arterial lesions, we could not examine the relation between chronic arterial lesions and the long-term risk of ischemic events. Yet none of the ischemic strokes and only one TIA that occurred after 6 months were associated with chronic arterial lesion. These findings do not support the use of invasive therapies such as surgery[20-22] or endovascular procedures[23-25] in the vast majority of patients with chronic arterial lesions.[9,17,18] The presence of multiple dissections at the acute stage of CAD was associated with a higher risk of subsequent stroke or TIA, but the 95% CI was wide.

The incidence of CAD recurrences is difficult to assess because some recurrences are asymptomatic, especially within the first weeks,[26] and dissections with isolated local signs are probably undiagnosed. In our study, the rate of symptomatic CAD recurrence (0.3%/year) is slightly lower than that reported in previous studies in which patients with connective tissue disease or a familial history of CAD accounted for the vast majority of recurrences.[6,7,27] Moreover, in one of these studies, dissection of renal artery accounted for part of recurrences.[7]

Appendix

Investigators of the Multicenter Survey on Natural History of Cervical Artery Dissection (by decreasing number of patients included). C.H. Sainte-Anne (Paris): D. Dimitri, E. Touzé, J.L. Mas, E. Méary, C. Oppenheim, J.F. Meder; CHRU Lille: M. Viallet, C. Lucas, D. Leys, J.Y. Gauvrit, X. Leclerc, J.P. Pruvo; CHU Rouen: P. Ahtoy, B. Mihout, E. Gérardin; CHU Nancy: J.C. Lacour, X. Ducrocq, S. Bracard; CHU Pitié Salpétrière: M. Obadia, Y. Samson, B. Marrot, C. Marsault; CHU Clermont–Ferrand: A. Coustes–Durieux, P. Clavelou, J. Gabrillargues; CH Meaux: A. Ameri, F. Chedru; CHU Marseille La Timone: L. Milandre, A. Ali Cherif, O. Levrier; CHU Bordeaux: I. Sibon, F. Rouanet, J.M. Orgogozo, P. Ménégon; CHU Tenon: C. Roos, E. Roullet, B. Marrot; CHU Angers: J.M. de Bray, F. Dubas, A. Pasco; CHU Dijon: G.V. Osseby, M. Giroud, D. Martin; CH Lens: F. Mounier–Vehier, D. Berthelot; CHU Besançon: F. Vuillier, T. Moulin, F. Cattin; CH Saint-Denis: T. Debroucker, C. Rouzier; CHU Tours: D. Saudeau, A. Autret, J.P. Cottier; Fondation Ophtalmologique A. de Rothschild: A. Bouchareine, O. Gout, P. Koskas; CH Mulhouse: G. Rodier, E. Cohen, D. Weisse; CHU Nîmes: P. Labauge, L. Jomir, A. Bonafé; CH Poissy: P. Tassan, H. Cambon, M. Molho; CH Bourges: E. Bodiguel, E. Pomet, A. Coatrieux; CHRU Amiens: S. Canaple, O. Godefroy, H. Deramond; CHU Limoges: F. Macian, J.M. Vallat, A. Maubon; CHU Brest: F. Rouhart, J.Y. Goas, M. Nonent.

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CME

The influence of diabetes and hyperglycemia on clinical course after intracerebral hemorrhage

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Abstract—*Objective:* To determine whether diabetes and admission hyperglycemia in nondiabetic patients influence outcome and the occurrence of cerebral and medical complications after intracerebral hemorrhage (ICH). *Methods:* The study sample included 764 patients with ICH. The effects of diabetes and admission hyperglycemia were examined in relation to 30-day and 3-month mortality using Cox regression models controlling for potential confounders. The analysis was conducted for the entire sample of patients and repeated in comatose and noncomatose patients. *Results:* Among comatose patients, neither diabetes nor admission hyperglycemia contributed significant predictive information, as nearly all patients died. In noncomatose patients, diabetes was an independent predictor of 30-day (odds ratio [OR] 1.31; 95% CI 1.08 to 1.58) and 3-month (OR 1.30; 95% CI 1.08 to 1.56) mortality and was associated with a greater incidence of infectious (OR 1.24; 95% CI 1.03 to 1.49) and cerebral (OR 1.42; 95% CI 1.10 to 1.83) complications. Among nondiabetic patients with Glasgow Coma Scale score of >8, hyperglycemia was an independent predictor of 30-day (OR 1.29; 95% CI 1.05 to 1.58) and 3-month (OR 1.27; 95% CI 1.05 to 1.53) mortality and was associated with a greater incidence of cerebral complications (OR 1.47; 95% CI 1.12 to 2.94). *Conclusions:* Both diabetes and admission hyperglycemia in nondiabetic patients are predictors of poor outcome after supratentorial ICH. This may be related to the greater incidence of cerebral and infectious complications in diabetic patients and of cerebral complications in hyperglycemic nondiabetic patients.

NEUROLOGY 2003;61:1351–1356

Diabetes mellitus, an independent risk factor for stroke and myocardial infarction, has also been associated with a worse clinical outcome in stroke patients[1-3] and myocardial ischemia.[4,5] Furthermore, hyperglycemia at the time of stroke in patients without a history of diabetes mellitus has been linked to a poor prognosis in populations of patients with cerebral ischemia[3,6-8] or mixed ischemic or hemorrhagic strokes[2,9] and in patients with cerebral infarction treated with thrombolytic drugs.[10-12]

Animal and human studies have elucidated some of the mechanisms of the detrimental effects of hy-

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Supported partly by grants from University of Siena, Italy.

Received May 15, 2003. Accepted in final form July 29, 2003.

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