

Association of Cervical Artery Dissection With Recent Infection

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Background: Cervical artery dissection (CAD) is an important cause of ischemic stroke in younger patients. However, its cause is insufficiently understood.

Objective: To test the hypothesis that CAD is frequently associated with recent infection.

Subjects and Methods: We compared the prevalence of infection during the preceding week in 43 consecutive patients with acute CAD and 58 consecutive patients younger than 50 years with acute cerebral ischemia from other causes (control patients). In subgroups of patients, we correlated infectious status with electron microscopic studies of skin biopsy specimens and investigated pathways potentially linking infection and CAD.

Results: Recent infection was more common in patients with CAD (25/43 [58.1%]) than in control pa-

tients (19/58 [32.8%]; $P = .01$). Respiratory tract infection was preponderant in both groups. Recent infection, but not the mechanical factors cough, sneezing, or vomiting, was independently associated with CAD in multivariate analysis. Investigation of serum antibodies against *Chlamydia pneumoniae*, smooth muscle cells, endothelial cells, collagen types I through IV, and heat shock protein 65 and assessment of serum α_1 -antitrypsin and HLA did not contribute to the understanding of the pathogenesis of CAD. More patients with pathologic findings in skin biopsy specimens tended to have had a recent infection (13/21 [62%]) than patients without pathologic findings (2/9 [22%]; $P = .11$).

Conclusion: Our results suggest a significant association between recent infection and CAD that is not explained by mechanical factors occurring during infection.

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CERVICAL ARTERY dissection (CAD) is increasingly recognized as an important cause of stroke and transient ischemic attack in young and middle-aged patients. In about 15% to 20% of younger patients, CAD may be the cause of cerebral ischemia.^{1,2} However, the pathogenesis of non-traumatic CAD is unclear. An underlying arteriopathy has often been presumed. In electron microscopic studies of skin biopsy specimens, we recently found evidence of abnormally structured collagen fibrils and/or elastin in about two thirds of patients with CAD.³ The aberrations consisted of collagen bundles with flowerlike cross sections and with numerous composite fibrils of variable, sometimes enlarged (in more severe cases) diameter. Elastic fibers showed minicalcifications and pronounced fragmentation in the most severe cases. Genetically determined alterations of the extracellular matrix may be an important predisposing factor for

CAD. However, such preexisting abnormalities do not explain all clinical features of this disease. Cervical artery dissection is characterized by a low rate of recurrence,⁴ and often there is simultaneous dissection of multiple cervical and sometimes also of renal arteries.^{5,6} Also, familiar occurrence is low. These observations suggest that short-lived trigger mechanisms may play an important role in the pathogenesis of CAD.

Several studies indicate that recent infection is among the most important risk factors for ischemic stroke in children and young adults.⁷⁻¹⁰ Recent observations in a few patients suggested that CAD may be associated with acute infection.^{11,12} Inflammatory mechanisms during infection and microbial agents themselves can cause substantial damage to the vascular wall.¹³⁻¹⁵ To test the hypothesis that recent infection may be a risk factor for CAD, we performed a prospective study comparing the prevalence of recent infection in consecutive patients

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SUBJECTS AND METHODS

During 2 years (April 1, 1994, to March 31, 1996), we examined 43 consecutive patients who were hospitalized for acute spontaneous CAD (**Table 1**). Patients with CAD associated with severe head or neck trauma were excluded. In all patients, diagnosis of CAD was confirmed by 1 or more of the following neuroradiological methods: digital subtraction angiography (n = 24), cervical magnetic resonance imaging and magnetic resonance angiography (n = 28), or computed tomographic angiography (n = 16). The diagnosis of dissection required 1 of the following criteria: (1) double lumen, (2) mural hematoma, (3) so-called string sign, or (4) long tapering occlusion or high-grade stenosis beginning several centimeters distal to the branching of the internal carotid (ICA) or vertebral arteries ("tapered sign").¹⁶ We compared results in patients with dissection with those in 58 consecutive patients younger than 50 years who were hospitalized for acute cerebral ischemia during 1 year (July 1, 1995, through June 30, 1996) (Table 1). The cause of cerebrovascular ischemia in control patients was classified as reported previously.¹⁷

We analyzed the history of infection within 1 week before CAD or ischemia in personal interviews by means of a standardized questionnaire that focuses on symptoms typical of infection. If patients could not be interviewed, the history was taken from their next of kin. The interview was done as soon as possible after admission. We diagnosed an infection as reported previously.^{10,11} Briefly, diagnosis required at least 1 typical symptom in combination with fever (temperature $\geq 38^{\circ}\text{C}$), subfebrile temperature (37.5°C - 37.9°C), or corresponding serological, cultural, or radiological findings indicating an acute infection. In addition, combinations of at least 2 typical corresponding symptoms were accepted. All subjects were asked about diseases that can mimic infectious disease, eg, an allergy. Combinations of signs and symptoms that may have been caused by diseases other than infection were not accepted. Furthermore, symptoms potentially caused by dissection, eg, cervical pain or pain radiating to the ears, were not considered. Bacterial infection was diagnosed when a potentially causative bacterium could be identified or when purulent secretion or technical findings typical of bacterial infection were present. In upper respiratory tract infection without evidence of bacterial infection, a viral cause was presumed. To be accepted, symptoms of infection had to have started before dissection or cerebral ischemia. The

following manifestations, if they developed acutely, were considered to indicate the beginning of dissection: pulsatile tinnitus, drooping eyelid, pupillary size difference, cervical or facial pain, symptoms of cranial nerve palsies, or central nervous system deficits.

To study the pathogenesis of infection-associated CAD, we performed several pilot studies in subgroups of patients. Serum samples from patients were stored at -80°C . For studies on *Chlamydia pneumoniae*, samples from patients with recent infection were chosen. For the other pilot studies, serum samples were randomly selected from all available samples. We determined serum levels of α_1 -antitrypsin by immunonephelometry (Behring, Marburg, Germany), antibodies against smooth muscle cells (IgG, IgA, IgM) by indirect immunofluorescence test (Mast, Reinfeld, Germany), and combined collagen types I through IV (IgG) by enzyme-linked immunosorbent assay (Euroimmun, Groß-Grönau, Germany). Antibodies against *C pneumoniae* (IgG, IgA, IgM) were determined by microimmunofluorescence test (J. T. Grayston, Seattle, Wash),¹⁸ antibodies against heat-shock protein 65 (hsp 65) by enzyme-linked immunosorbent assay (G. Wick, Innsbruck, Austria),¹⁹ and antibodies against endothelial cells as described previously (W. Schmidt, Lübeck, Germany).²⁰ The HLA typing was performed from fresh venous blood by the standard National Institutes of Health microlymphocytotoxicity test for HLA class I antigens (Biotest, Dreieich, Germany) and by DNA analysis for HLA-DRB1 alleles.^{21,22}

In a post hoc analysis, we compared infectious status with results from parallel electron microscopic studies of the structure of collagen and elastin in skin biopsy specimens in 30 patients with CAD. Electron microscopic studies were performed as described recently.³

The study was approved by the ethics committee of the University of Heidelberg, Heidelberg, Germany. Subjects gave informed consent.

To compare sample proportions, we used the χ^2 or Fisher exact test as appropriate. Bonferroni correction was applied for the analysis of HLA data. We used the Mann-Whitney *U* test to compare continuous variables and the binomial test to analyze the seasonal distribution of diseases. We defined October to March a priori as the cold season and April to September as the warm season in Germany. Multiple logistic regression analysis was used to simultaneously analyze the influence of multiple factors on a variable. We used the statistical software package SAS (SAS Institute Inc, Cary, NC) for the analyses.

with CAD and in younger patients with cerebral ischemia from other causes. In patients with CAD who had undergone skin biopsies, we correlated infectious status with biopsy results. Furthermore, we performed several pilot studies investigating various hypotheses of possible inflammatory or immunological mechanisms in the pathogenesis of CAD.

RESULTS

The 43 patients with CAD had dissections of 51 extracranial arteries. Table 1 shows the arteries involved and clinical symptoms in patients with CAD. Extracranial Doppler sonograms were abnormal in all 43 patients. Patho-

logic patterns included a high-resistance flow pattern and stenosis or occlusion distal to the ICA origin. Nine patients reported recent minor trauma or particularly strenuous physical work. In 16 patients, first symptoms of dissection occurred on the day of admission; in 13 patients, between 2 and 7 days before admission; and in 14 patients, more than 1 week before admission. Table 1 also gives the cause of cerebral ischemia among control patients. All 20 patients with unknown causes had normal extracranial Doppler sonograms, and 8 of these patients additionally underwent magnetic resonance angiography or computed tomographic angiography to exclude CAD. **Table 2** shows demographic data and vascular risk factors in both groups.

Table 1. Clinical Features in Both Groups

	No. (%) of Patients
Patients With Cervical Artery Dissection (n = 43)	
Brain-supplying arteries dissected	
Internal carotid artery	
Right	13 (30)
Left	12 (28)
Both	4 (9)
Vertebral artery	
Right	4 (9)
Left	8 (19)
Both	1 (2)
All 4 brain-supplying arteries	1 (2)
Clinical symptoms	
Ischemic stroke	28 (65)
Transient ischemic attack	5 (12)
No cerebral ischemia*	10 (23)
Control Patients (n = 58)	
Clinical symptoms	
Ischemic stroke	47 (81)
Transient ischemic attack	11 (19)
Cause of cerebral ischemia	
Cardioembolism	18 (31)
Arterioarterial embolism from large artery atherosclerosis	12 (21)
Cerebral vasculitis	1 (2)
Cerebral microangiopathy	1 (2)
Presumed hypercoagulopathy in association with	
Metastasizing bronchial carcinoma	1 (2)
Protein C deficiency	1 (2)
Combinations of smoking, oral contraceptives, migraine, or childbirth in young women	4 (7)
Unknown	20 (34)

*Only pulsatile tinnitus, nerve compression syndromes, or facial, cervical, or cranial pain.

Infection in the preceding week was more common in patients with CAD (25/43 [58.1%]) than in the control group (19/58 [32.8%]; $P = .01$). Seven (70%) of 10 patients with CAD without cerebral ischemia and 18 (54.5%) of 33 patients with CAD with cerebral ischemia (comparison with the control group, $P = .04$) had had an infection. In univariate analysis, patients with CAD and control patients differed with respect to diabetes mellitus, smoking, and social status (Table 2). In multivariate analysis with current smoking and high social status, infection remained significantly associated with CAD ($P = .02$; **Table 3**). Diabetes mellitus could not be included in the model because none of the patients with CAD had this factor. Respiratory tract infection was preponderant in both groups (**Table 4**). Patients with CAD with upper respiratory tract infection ($n = 17$) had purulent tonsillitis, purulent and nonpurulent pharyngitis ($n = 2$), otitis media ($n = 2$), and sinusitis as diagnosed by their physicians or combinations of cough, rhinitis, hoarseness, and increased body temperature ($n = 11$). In 15 patients with CAD (35%) and in 5 control patients (9%; $P = .003$), infection had been diagnosed and treated by physicians before dissection or ischemia. Various potentially causative microbes were identified in patients with CAD (*Staphylococcus aureus*, influenza virus type B, *Enterovirus*, and cytomegalovirus) and in control patients (*S aureus*, *Haemophilus influenzae*, *Mycoplasma pneu-*

Table 2. Age, Sex, and Risk Factors in Both Groups*

Age, Sex, and Risk Factors	Patients With Dissection (n = 43)	Control Patients (n = 58)	P
Age, y	43.7 ± 9.0	41.4 ± 7.2	.35
Female sex	15/43 (35)	21/58 (36)	.84
Hypertension	12/43 (28)	23/58 (40)	.22
Diabetes mellitus	0/43 (0)	6/58 (10)	.04
Current smoking	15/43 (35)	34/58 (59)	.02
Hyperlipidemia†	11/43 (26)	16/58 (28)	.82
Oral contraceptives	6/15 (40)	5/21 (24)	.50
High social status‡	15/43 (35)	4/58 (7)	<.001
Medium social status§	23/43 (54)	45/58 (78)	.01
Low social status	5/43 (12)	9/58 (16)	.77

*All values are given as number (percentage), except age (mean ± SD).

†Hypertriglyceridemia and/or hypercholesterolemia.

‡Subjects whose professional activity requires academic or similar training.

§Subjects whose professional activity requires specific, but nonacademic, training.

||Subjects whose professional activity does not require special training and subjects without completed school education.

moniae, *Streptococcus*, mumps virus, influenza virus type A, parainfluenzavirus, and Coxsackievirus type B).

Both infection with and without cough, sneezing, or vomiting tended to be more common in patients with CAD than in the control group (Table 4). In multivariate analysis, infection within 1 week (odds ratio, 2.42; 95% confidence interval, 1.01-5.80; $P = .05$) but not cough, sneezing, or vomiting (odds ratio, 1.60; 95% confidence interval, 0.67-3.80; $P = .29$) was associated with CAD. Cervical artery dissection was more often diagnosed during the cold season ($n = 28$) than during the warm season ($n = 15$) ($P = .05$; infection-associated CAD, $n = 21$ vs $n = 4$; $P = .002$). The prevalence of cerebral ischemia in the control group was not different between the cold season ($n = 28$; infection-associated ischemia, $n = 11$) and the warm season ($n = 30$; infection-associated ischemia, $n = 8$). In patients with CAD, the rate of infection was similar in the first (13/21 [61.9%]) and second (12/22 [54.5%]) years of the recruitment period.

Titers of IgG-class antibodies against *C pneumoniae* were similar between patients with infection-associated CAD ($n = 25$; median, 1:32; range, 0-1:1024) and 15 healthy age- and sex-matched control subjects from the same area ($n = 15$; median, 1:32; range, 0-1:512). IgG titers indicating acute infection ($\geq 1:512$) and IgM- and IgA-class antibodies did also not show differences between groups. Titers of antibodies against hsp 65 were not higher in patients with CAD ($n = 18$) than in control subjects ($n = 21$), neither in subjects with recent infection ($n = 10$; median, 1:640; range, 1:320-1:2560 vs $n = 11$; median, 1:640; range, 1:160-1:1280) nor in those without recent infection ($n = 8$; median, 1:640; range, 1:320-1:1280 vs $n = 10$; median, 1:480; range, 1:320-1:640). Likewise, patients with CAD did not have higher titers of antibodies against smooth muscle cells ($n = 40$; median, 1:40; range, 1:20-1:80) than control patients ($n = 29$; median, 1:40; range, 0-1:160). None of 20 patients with CAD tested positive for anti-endothelial cell antibodies. Antibodies against collagen types I through IV were

Table 3. Conditional Logistic Regression Analysis With Infection Within 1 Week, Current Smoking, and High Social Status*

Factor	OR (95% CI)	P
Infection within 1 wk	2.87 (1.18-7.00)	.02
Current smoking	0.49 (0.18-1.05)	.06
High social status	6.54 (1.88-22.7)	.003

*OR indicates odds ratio; CI, confidence interval.

slightly increased in 3 (23-35 relative units per milliliter; normal values, <20 U/mL) and highly increased in 1 (326 U/mL) of 41 patients with CAD. None of 16 patients with acute CAD and none of 19 patients tested more than 3 months after CAD had abnormally low (<1.4 g/L) serum levels of α_1 -antitrypsin. As compared with a control group of healthy, local blood donors (n = 287), HLA-Cw3 was found more frequently in patients with CAD (36.2% vs 21.3%), whereas HLA-DR17 (serological analysis; equals DRB1*0301 in DNA analysis) appeared less frequently (6.4% vs 19.2%). However, these differences were not significant after correction for multiple tests. No other association between any alleles and either CAD or infection-associated CAD was observed. Skin biopsy specimens were examined by electron microscopy in 30 patients with CAD, 15 with and 15 without recent infection. Structural abnormalities were found in 21 patients (70%). Patients with pathologic skin biopsy specimens more often tended to have had a recent infection (13/21 [62%]) than patients without pathologic findings (2/9 [22%]; P = .11).

COMMENT

The high rate of recent infection (33%) in our control group of younger patients with cerebral ischemia is in accordance with former studies reporting prevalences between 25% and 42%.^{7,10,11,23} In our previous investigations, the prevalence of infection within the preceding week was much lower both in hospital controls with non-vascular and noninflammatory neurological diseases (8.4%)¹⁰ and in control subjects randomly selected from the population (5.1%).¹¹

This result adds to the evidence that acute infection is among the most important risk factors for cerebral ischemia in younger age groups. Despite the high prevalence among control patients in this study, recent infection was still significantly more common in patients with CAD. In many cases, physicians not involved in our study had diagnosed the infection before CAD occurred. The first symptoms of dissection occurred sometimes several weeks before admission, whereas all patients from the control group were admitted shortly after ischemia. Because earlier antecedent events are less easily remembered, the prevalence of infection before CAD may still be underestimated. The rate of infection underlies a seasonal variation; therefore, the recruitment period in both groups covered 1 whole year and 2 whole years, respectively. We diagnosed CAD less often between May and October than between Novem-

Table 4. Characterization of Infection in Both Groups

Variable	No.		P
	Patients With Dissection (n = 43)	Control Patients (n = 58)	
Location of infection			
Respiratory tract	22	15	.009
Upper respiratory tract*	17	12	
Purulent bronchitis	5	2	
Pneumonia	0	1	
Purulent dental infection	2†	1	
Gastrointestinal tract	1	1	
Other	2	2	
Any infection	25	19	.01
Cause of infection			
Evidence of bacterial infection	9	6	.14
Probably viral	16	15‡	.22
Symptoms of infection			
Increased body temperature ($\geq 37.5^\circ\text{C}$)	9	6	.14
Patients with infection			
With cough, sneezing, or vomiting	17	14	.10
Without cough, sneezing, or vomiting	8	5	.14
Patients with or without infection			
Cough, sneezing, or vomiting§	26	24	.06

*Including 1 patient in each group with influenza infection and predominant symptoms of upper respiratory tract infection.

†Both patients had a dental and a respiratory tract infection during the preceding week.

‡Two patients had evidence of simultaneous bacterial and viral infection.

§Some subjects in both groups reported on recent cough, sneezing, or vomiting without further evidence of acute infection, including patients with chronic cough caused by smoking and subjects with isolated symptoms in whom a diagnosis of acute infection was not made.

ber and April, when respiratory infection is more common in our country. A role of infection in the pathogenesis of CAD could explain this seasonal distribution pattern. An annual variation of the prevalence of infection could have influenced the differences between groups. However, the similar infection rate in both years of the recruitment period in patients with CAD indicates that this probably did not have an important impact.

Some case reports mentioned influenzalike syndromes, other febrile diseases, or increased inflammatory measures in patients with CAD,^{5,6,24-27} but infection has not been regarded as an important pathogenetic factor in CAD so far. Minor trauma and unusual physical exercise are considered trigger factors for CAD. Infection is often associated with events causing mechanical stress to cervical arteries, such as cough, vomiting, and intensive sneezing. However, in our multivariate analysis, a diagnosis of recent infection but not cough, sneezing, or vomiting was independently associated with CAD. As such mechanical factors occur frequently, they could not explain the low recurrence rate of CAD. Thus, mechanical stress does not sufficiently explain the association between infection and CAD.

Histological studies have seldom detected slight adventitial inflammation in the vessel wall in CAD.²⁴ Therefore, CAD is not regarded as inflammatory arteriopathy.

In contrast, investigations in intracranial²⁸⁻³¹ and coronary³²⁻³⁴ dissection often showed inflammatory infiltrates in the arterial wall. Rapid death after intracranial and coronary dissection may disclose pathologic alterations that may have already disappeared when specimens of extracranial dissection were investigated. Furthermore, nonatherosclerotic aneurysms of coronary arteries are often accompanied by a prodromal "influenzalike syndrome" and inflammatory alterations of the vessel wall on autopsy.³⁵ Cervical and peritonsillar infection can cause true aneurysms of the ICA, probably by spreading of the inflammation to the arterial wall.^{36,37} Such a paradigm may apply to some of our patients with infection-associated CAD, eg, to 2 patients with pharyngitis.

During infection, several mechanisms including pro-inflammatory cytokines, free radicals, and proteases can damage the vessel wall.^{15,38} Increased levels of C-reactive protein and proinflammatory cytokines can induce a procoagulant state during infection.^{39,40} Therefore, one may argue that infection favors thrombotic complications after dissection but may not contribute to the pathogenesis of dissection itself. However, the prevalence of recent infection was also high among the 10 patients with CAD without thromboembolic complications after dissection. Recently, a patient with α_1 -antitrypsin deficiency and ICA dissection was described.⁴¹ Reduced antiproteolytic protection could contribute to vascular lesions during infection. Immunization with hsp 65, a stress protein expressed during infection, can induce atherosclerotic lesions. Increased antibody titers against hsp 65 were found in patients with atherosclerotic ICA stenosis.^{19,42} Dissection occurs in the tunica media, and increased antibodies against smooth muscle cells can be found during infection.⁴³ However, our pilot studies did not indicate that decreased serum levels of α_1 -antitrypsin or antibodies against hsp 65, smooth muscle cells, endothelium, or collagen types I through IV are important contributors to the pathogenesis of CAD. Recent studies indicated that ischemic stroke in children and the moyamoya disease may both be associated with HLA-B51 and with infectious disease.^{44,45} Molecular mimicry between microbial antigens and HLA antigens could link infection, vascular injury, and the HLA system. Our results do not show an association between certain HLA alleles and CAD. Infection with *C pneumoniae* may contribute to atherogenesis,⁴⁶ whereas our data do not suggest a role of *C pneumoniae* in the pathogenesis of CAD. However, it is still possible that other microbial agents may contribute to dissection.

Our recent results hint at abnormalities of extracellular matrix proteins as an important predisposition to CAD.³ Interestingly, there was a trend toward an association between abnormalities in skin biopsy specimens and recent infection. It is tempting to speculate that pre-existing abnormalities of extracellular matrix proteins may increase the susceptibility to infection-associated injury of the arterial wall. However, the number of subjects investigated was small, and the comparison between infectious status and skin biopsy results was a post hoc analysis. Therefore, further data are required. In conclusion, the frequent association of recent infection and CAD suggests the existence of infection-related mechanisms

leading to CAD, but the nature of these mechanisms is incompletely understood at present.

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