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A Systematic Review of the Risk Factors for Cervical Artery Dissection

Sidney M. Rubinstein, MSc; Saskia M. Peerdeman, MD, PhD; Maurits W. van Tulder, PhD; Ingrid Riphagen, MSc; Scott Haldeman, MD, PhD

Background and Purpose—Cervical artery dissection (CAD) is a recognized cause of ischemic stroke among young and middle-aged individuals. The pathogenesis of dissections is unknown, although numerous constitutional and environmental risk factors have been postulated. To better understand the quality and nature of the research on the pathogenesis of CAD, we performed a systematic review of its risk factors.

Methods—PubMed [MEDLINE (1966 to February 22, 2005)] and Embase (1980 to February 22, 2005) were searched to identify studies fulfilling the inclusion criteria. Two reviewers independently assessed methodological quality of the primary studies. Relevant data were extracted, including the risk factor(s) investigated, characteristics of the study population, and strength of the association(s).

Results—Thirty-one case-control studies were included for analysis. Selection bias, lack of control for confounding, and inadequate method of data analysis were the most common identified methodological shortcomings. Strong associations were reported from individual studies for the following risk factors: aortic root diameter >34 mm (odds ratio [OR]=14.2; 95% confidence interval [CI], 3.2 to 63.6), migraine (OR_{adj}, 3.6; 95% CI, 1.5 to 8.6), relative diameter change (>11.8%) during the cardiac cycle of the common carotid artery (OR_{adj}, 10.0; 95% CI, 1.8 to 54.2), and trivial trauma (in the form of manipulative therapy of the neck) (OR_{adj}, 3.8; 95% CI, 1.3 to 11). A weak association was found for homocysteine (2 studies: OR_{crude}, unknown; 95% CI, 1.05 to 1.52; OR_{crude}, 1.3; 95% CI, 1.0 to 1.7), and recent infection (OR_{adj}, 1.60; 95% CI, 0.67 to 3.80). Two studies had conflicting findings for low levels of α_1 -antitrypsin, with the methodologically stronger study suggesting no association with CAD.

Conclusions—CAD is a multi-factorial disease. Many of the reviewed studies contained 2 or more major sources of bias commonly found in case-control studies. Only one study (of homocysteine) used healthy controls, a robust sample size, and had a low risk of biased results. The relationship between atherosclerosis and CAD has been insufficiently examined. (*Stroke*. 2005;36:1575-1580.)

Key Words: carotid arteries ■ cerebral artery disease ■ dissection ■ vertebral artery

Cervical artery dissection (CAD) is an increasingly recognized cause of ischemic stroke among the young and middle-aged.^{1,2} The reason why these dissections occur in otherwise healthy-appearing young individuals either spontaneously or after common daily activities remains unknown, although numerous risk factors have been postulated (eg, connective tissue disorders,³⁻⁷ hyperhomocystinemia,⁸⁻¹⁰ recent infection,¹¹⁻¹³ α_1 -antitrypsin [α_1 -AT],¹⁴ and a variety of common neck movements¹⁵⁻¹⁸).

It is easy to postulate why certain risk factors may predispose a patient to dissection. Connective tissue provides mechanical stability and elasticity to the vessel wall.¹⁹ Structural impairments, caused by damaged or abnormally formed collagen and elastic fibers, could lead to weaknesses at points of decreased resistance, thus resulting in rupture.³ Similarly, α_1 -antitrypsin is a proteinase inhibitor of enzymes that con-

tributes to the integrity of the connective tissue.¹⁴ Deficiency in α_1 -AT could result in degradation of the vessel wall through inadequate protection. Other risk factors are more difficult to explain. For example, whereas hyperhomocystinemia has been shown to cause endothelial damage,^{20,21} CAD is not the result of endothelial disease. Additionally, it is difficult to understand how a recent infection, trivial trauma, or common neck movements, which are pervasive in society and rarely associated with CAD, could be anything more than a trigger in a susceptible individual.^{11-13,16}

Therefore, to better understand the pathogenesis of dissection, we performed a systematic review of the risk factors for CAD.

Patients and Methods

Study Selection

Cohort and case-control studies were identified by searching PubMed [MEDLINE (1966 to February 22, 2005)] and Embase

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From the Institute for Research in Extramural Medicine (EMGO; S.M.R.), Department of Neurosurgery (S.M.P.), Institute for Health Sciences (M.W.v.T.), Library (I.R.), Vrije University Medical Center, Amsterdam, the Netherlands; and the Department of Neurology (S.H.), University of California, Irvine, Department of Epidemiology, School of Public Health, University of California, Los Angeles.

Correspondence to Sidney Rubinstein, MSc, 1e Heezerlaantje 2a, 3766 LW Soest, the Netherlands. E-mail SM.Rubinstein@vumc.nl

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(1980 to February 22, 2005). The search strategy, which was developed by an experienced librarian (I.R.), used the following MESH headings: "carotid artery, internal, dissection" (OR) "vertebral artery dissection," combined (Boolean AND) with "risk factors" (OR) "epidemiologic methods" (OR) "causality," and finally combined (Boolean NOT) with surgery (OR) animal. Additionally, relevant combinations of free text search terms were used in PubMed (MEDLINE), whereas a similar strategy was used in Embase. The precise construction of the search is available on request from the primary author (S.M.R.). No restrictions were applied on the year of publication, language, the type of risk factor, age, or gender of the subject. All abstracts that met our search strategy were examined. To limit publication bias, the references of all primary studies were also inspected for studies potentially missed in the electronic search.

The first reviewer (S.M.R.) was responsible for the entire selection process, whereas a second reviewer (M.W.v.T.) evaluated the reproducibility of the selection process by selecting a random sample ($n=100$) from the articles identified in PubMed (MEDLINE). Justification for excluding studies was also noted. The 2 reviewers (S.M.R., M.W.v.T.) then reviewed the selected studies and assessed whether they fulfilled the inclusion criteria.

Inclusion and Exclusion Criteria

A study was included in this review if: (1) the study population included subjects with a confirmed or an assumed diagnosis of CAD; (2) a control group (or noncases) were also included; (3) at least 1 risk factor was measured for all subjects; and (4) the publication was a full report. The following studies were excluded: case reports or case series; abstracts and letters to the editor; dissections because of surgical or angiographic procedures; and major trauma dissections.

Methodological Quality Assessment

The quality of the included studies was evaluated by means of a criteria list (Table).²²⁻²⁴ Two reviewers (S.M.R., S.M.P.), each blind to the other's assessment, scored the criteria items according to the presence or absence of that item in the study, whereas inadequately described items or items that were not applicable were also noted. The reviewers subsequently met to discuss and reach agreement on differences in coding during a consensus meeting. A third reviewer was consulted (M.W.v.T.) when necessary.

Instead of calculating a validity score from the quality assessment, we chose to address the types of bias present in the various studies. Some authors have criticized an overall score, demonstrating that a score virtually ignores the importance of individual quality items. The result may be that specific shortcomings may become diluted²⁵ or biased.²⁶

Data Extraction

Individual study characteristics were also extracted by the reviewers, using a predetermined form. Extracted data included: characteristics of the study population, the risk factors measured, potential confounders, and strength of the associations.

Data Analysis

Studies were included only once if there were multiple publications, which was the case for infection.^{12,27} Crude odds ratios (OR_{crude}) and adjusted odds ratios (OR_{adj}) are presented. Data were not pooled because of heterogeneity with regard to study population, risk factors, and analyses (eg, crude versus adjusted ORs).

Results

Study Selection

A total of 922 abstracts were identified in PubMed (MEDLINE) that met our search criteria, whereas an additional 101 abstracts were found in Embase. From this search, 45 studies were identified for possible inclusion (all from MEDLINE), and these articles were reviewed in detail. An additional study was identified through reference checking that was not found in the electronic search.²⁸

Methodological Criteria for Assessing the Quality of Studies on Risk Factors for Cervical Artery Dissection

Methodological Criteria

Objective of the study

A. Positive if the hypothesis and/or the objective of the study is clearly defined

Study population

B. Positive if the main features of the study population were stated

C. Positive if the inclusion/exclusion criteria of the study population was clearly stated to enable replication of the study

D. Positive if controls were age- and sex-matched, recruited in the same time frame as the cases, and were noncerebrovascular stroke cases

E. Positive if subjects were consecutively included

Description of potential confounders

F. Positive if comorbidity or concomitant disease, such as vascular risk factors, were reported and presented in the data

Assessment of risk factors

G. Positive if the risk factors to be measured were clearly defined

H. Positive if the outcome instruments used to determine the presence of the risk factor/exposure were valid and reliable

Assessment of outcome/disease (CAD)

I. Positive if the main outcome/disease to be measured (CAD) was clearly defined and the diagnosis for the cases was confirmed

Blinded assessment

J. Positive if determination of exposure was strictly applied without knowledge of outcome/disease status, when necessary

Data analysis and presentation

K. Positive if the methods of statistical analysis were appropriately used and measures of association were estimated (including confidence intervals)

L. Positive if a stratified or multivariable analysis was used and potential confounders were used in the analysis

M. Positive if the number of cases examined in the final multivariable model were at least 10-times the number of independent variables used in the analysis

A '+' or '-' was assigned for those items that did or did not meet the criteria, respectively. A '?' or 'N/A' was used in those cases in which either the item was unclear or not applicable to that study.

After discussion and consensus, 31 articles were selected which examined 8 risk factors.^{3,4,9,10,12-14,27-50} All of the identified studies used a case-control design. A number of case-series as well as cohorts of dissection were identified and excluded because they did not include a control group of noncases.⁵¹⁻⁵⁸ Two studies included cases of trivial trauma.^{9,37} Two separate studies used data from the same cases to examine different risk factors, namely infection and migraine.^{13,46}

Methodological Quality Assessment

The results of the methodological evaluation are presented in Table I (available online only at <http://www.strokeaha.org>).

The most common methodological flaw was selection bias, items D and E (45% and 61% of the studies, respectively). While most studies used adequate instruments to evaluate exposure (item H: 94%), only half of the studies used "blinded assessment" (when necessary) to evaluate exposure data (item J: $n=5/10$, 50%). Only 35% of the studies (item L) conducted stratified or multivariate analyses. Additionally, only 2 studies included sufficient numbers of cases in their regression analysis (item M: 6%), and only approximately half of the studies (52%) listed additional confounders other than age and gender (item F).

Study Characteristics

Data were extracted and are presented in Table II (available at <http://www.strokeaha.org>).

Risk Factors for CAD

We classified risk factors for CAD into 4 categories listed here. Fourteen studies were identified that examined either the association of gene polymorphisms with CAD or conducted a sequencing analysis to identify unknown gene pathogenic mutations.* Additional studies examined α_1 -AT,^{12,14,38} connective tissue disorders,^{3,4,36} hyperhomocystinemia,^{9,10,37,42} migraine,^{28,31,46} manipulative therapy of the neck,^{43,44} recent infection,^{12,13,27} and vessel abnormalities.^{28–30,40,45} Many studies examined secondary risk factors, such as those associated with atherosclerosis.†

Genetic or Inborn Predisposition/Disorders With a Familial Association

α_1 -AT

One small study ($n=22$ cases) found low levels of α_1 -AT to be strongly associated with CAD (OR_{adj}, 17.7; 95% CI, 2.9 to 105.6),¹⁴ which is in contrast with a much larger study ($n=80$ cases),³⁸ as well as the study by Grau et al.¹² Selection bias, small sample size, and lack of description of the study population were the main methodological shortcomings in the study by Vila et al,¹⁴ whereas Konrad et al used a robust sample size and a population-based control group.³⁸ Additionally, Konrad et al³⁸ found that the α_1 -AT genotypes did not differ among cases and controls, as did Grond-Ginsbach et al.³⁵

Connective Tissue Disease

Three studies were identified from the same research group, with the same subjects being included in subsequent larger studies.^{3,4,36} Connective tissue abnormalities were present in 55% ($n=36/65$)⁴ and 68% ($n=17/25$)³ in 2 studies, whereas none of the non-CAD ischemic controls in either study demonstrated such abnormalities. The study by Hausser et al did not evaluate risk.³⁶ Selection bias,^{3,4} lack of description of potential confounders,^{4,36} and lack of multivariate analysis were the principal shortcomings.^{3,4,36}

Gene-association Studies

Polymorphisms of the following genes were examined for their association with CAD: α_1 -AT deficiency alleles (PiZ,

PiS), ABCC6, CBS 844ins68bp, IL-6 promoter variants, the matrix metalloproteinase-9 gene, *MTHFR* C677T, and *MTHFD1* G1958A.^{9,10,35,37,41,49,50} Pezzini et al found the homozygous *MTHFR* TT genotype to be strongly associated with CAD (OR, unknown; 95% CI, 1.10 to 19.23)¹⁰; however, a subsequent and methodologically stronger study did not confirm these findings,³⁷ as well as the study by Gallai et al.⁹ The remaining polymorphisms were not found to be associated with CAD.

Gene Mutation/Sequencing Studies

The following genes were examined for possible unknown pathogenic mutations and their role in CAD: *COL3A1*, *COL5A1*, *COL5A2*, *COL8A1*, *COL8A2*, and *ELN*.^{32–34,39,47,48} None of the identified mutations, however, was suggested to play a major role in the cause of CAD.

Methodological shortcomings were identified in many areas and in numerous of the gene association/gene mutation studies, including, for example, lack of description of the study population (criteria B: 43%),^{32,34,35,41,48,50} lack of a clear inclusion/exclusion criteria (criteria C: 43%),^{32,34,39,41,49,50} no description of possible confounders (criteria F: 64%),^{32–35,39,41,48–50} as well as possible selection bias (criteria E: 78%)^{32–34,37–39,41,47–50} and lack of a clear statistical analysis and presentation (criteria K: 43%).^{10,32–34,41,48}

Homocysteine

Two studies reported a weak association (OR, unknown; 95% CI, 1.05 to 1.52),¹⁰ (OR_{crude}, 1.33; 95% CI, 1.04 to 1.70).³⁷ In subanalysis, a strong association was found for plasma homocysteine concentration >12 $\mu\text{mol/L}$ among cases (OR_{crude}, 11.02; 95% CI, 2.25 to 44.23).¹⁰ Shortcomings included selection bias,¹⁰ and lack of multivariate analysis or inclusion of sufficient cases.^{9,10,42}

Migraine

Tzourio et al found a strong association (OR_{adj}, 3.6; 95% CI, 1.5 to 9.6) among cases as compared with non-CAD ischemic stroke.⁴⁶ Similarly, d'Anglejean-Chatillon et al found migraine to be more common in cases than healthy subjects ($P<0.05$),³¹ as did Guillon et al ($P=0.005$).¹³ Shortcomings included selection bias,^{13,46} lack of blinded assessment,^{31,46} and lack of a multivariate analysis.^{13,31}

Vessel Abnormalities

Guillon et al found a relative diameter change ($>11.8\%$) during the cardiac cycle for the common carotid artery to be associated with ICAD (OR_{adj}, 10.0; 95% CI, 1.8 to 54.2).²⁸ Endothelium-dependent vasodilation was found to be significantly impaired in CAD,⁴⁰ whereas another study found abnormal elastic properties in CAD subjects.³⁰ Aortic diameter (>34 mm) was associated with dissection in another study (OR, 14.2; 95% CI, 3.2 to 63.6).⁴⁵ Redundant internal carotid arteries ($P=0.0019$), bilateral redundancies ($P=0.0001$), and number of redundant vessels ($P=0.009$) were also identified as risk factors.²⁹ Shortcomings included selection bias,^{29,40,45} lack of blinded assessment,²⁹ and potential confounding.^{29,40}

Environmental Exposures

Infection

Data from one study¹² were used in a subsequent study.²⁷ Acute infection was more prevalent in cases than non-CAD

*References 9, 10, 32–35, 37–39, 41, 47–50

†References 3, 4, 9, 10, 12–14, 27–31, 37, 38, 40, 44, 46, 47

ischemic controls (OR_{crude}, 3.0; 95% CI, 1.1 to 8.2;¹³ OR_{crude}, 2.4; 95% CI, 1.01 to 5.80¹²). However, when adjusted for the mechanical stress associated with coughing, sneezing, or vomiting, this lowered the OR (OR_{adj}, 1.60; 95% CI 0.67 to 3.80), suggesting only a weak association.¹² Forms of bias included: selection bias,^{12,13} lack of blinding,¹² and lack of a stratified analysis.¹³

Oral Contraceptive Use

No case-control studies were identified; however, oral contraceptive use was positively associated with CAD in 3 studies in bivariate analysis.^{12,31,46} In only 1 study was the association statistically significant ($P < 0.001$).³¹

Trauma

Trivial Trauma

No case-control study was identified, although trivial trauma is frequently cited in large cohorts of dissection (prevalence, range: 12% to 34%).^{52–55,58} Because there were 2 studies on manipulative therapy of the neck, this procedure was used as a proxy for trivial trauma.^{43,44} A strong association was found for manipulative therapy (OR_{adj}, 3.8; 95% CI, 1.3 to 11).⁴⁴ However, although an important confounder (ie, neck pain before the onset of stroke) was adjusted for in regression analysis, selection and information bias⁴⁴ were most probably present. The study by Rothwell et al lacked control for confounding and included cases of occlusive stroke along with unconfirmed dissections.⁴³ The number of cases identified in both studies were few ($n=7$),^{43,44} and in only 57% ($n=4/7$) of the cases was there a clear temporal association between the treatment and the onset of dissection (using 24 hours after the treatment as the cutoff point).^{43,44}

Risk Factors for Atherosclerosis

Vascular Risk Factors

Numerous studies measured the various risk factors commonly associated with atherosclerosis, namely, hypertension, diabetes, smoking, oral contraceptive use, and/or cholesterol levels.‡ In general, CAD was less likely to be associated with the vascular risk factors than non-CAD ischemic stroke. Specifically, these control subjects were significantly associated with coronary artery disease ($P=0.029$),⁴⁴ diabetes mellitus ($P=0.04$),¹² hypercholesterolemia ($P=0.005$),¹³ hypertension ($P=0.011$),²⁹ were current smokers ($P=0.02$),¹² and had “vascular risk factors” (not further defined) ($P=0.01$).¹⁴ Multivariate analysis suggested a negative association for the “vascular risk factors” (OR_{adj}, 0.14; 95% CI, 0.34 to 0.65),¹⁴ as was suggested by Grau et al for “current” cigarette smoking (OR_{adj}, 0.49; 95% CI, 0.18 to 1.05; $P=0.06$),¹² and Konrad et al for diabetes (OR_{crude} = 0.79; $P=0.8$).³⁷ However, Konrad et al found smoking (OR_{crude}, 1.28; $P=0.48$) and hypertension (OR_{crude}, 2.06; $P=0.08$) to be associated with risk.³⁷

Age

Numerous studies have shown that CAD occurs in a much higher frequency in young individuals (younger than age 45) when the risk of atherosclerosis is modest, whereas athero-

sclerosis increases exponentially with age when the risk of CAD is rare.^{1,2,14,43,54–57}

Discussion

To better understand pathogenesis of CAD, we conducted a systematic review. A methodological quality assessment has never been conducted on this topic. In all, 31 studies were identified and included. All but 1 study have been published in the past 10 years,³¹ most probably reflecting advances in technology and increased recognition of dissection.⁵⁹

Although a number of associated and potential risk factors have been identified in cohorts of dissection, we found little evidence to support their presumed risk. For example, although the vascular risk factors are risk factors for ischemic stroke^{60,61} and are commonly reported in cohorts of dissection,^{51–56,58} it is not clear whether they pose an increased risk in CAD. In fact, some of the vascular risk factors may even be protective. This observation, however, has ramifications for what one considers an appropriate control in case-control studies. As one author has noted, CAD is not an atherosclerotic disease.⁶² In our review, we considered healthy age- and sex-matched subjects suitable controls. However, many of the reviewed studies used patients with other forms of stroke as controls.^{3,4,10,12–14,27,40,44–46} In many of the studies, risk factors associated with atherosclerosis tended to favor the controls, consisting of non-CAD ischemic stroke. The relationship between CAD and risk factors for atherosclerosis, however, is most probably a complex one. Despite the fact that moderately elevated plasma homocysteine levels are an independent risk factor for atherosclerosis,⁶³ one study failed to identify atherosclerotic lesions in younger CAD subjects with mild hyperhomocystinemia.⁶⁴ We therefore suggest that those studies that used non-CAD ischemic stroke as a control may have been subject to selection bias and therefore may have overestimated risk.

Although trivial trauma is an often presumed cause of CAD, we did not find any studies that suggest that common neck movements pose an independent risk for CAD. Whereas manipulative therapy of the neck is a commonly reported risk factor for CAD (range, 3% to 30%),^{52,54,55,65} we identified only 2 studies which were able to access risk, and one of those contained 2 major forms of bias.⁴⁴ The remaining study included unconfirmed cases of dissection and occlusive stroke.⁴³ Furthermore, the exceptionally small number of cases in both studies ($n=7$)^{43,44} accounts for only a very small percentage of CAD cases. Therefore, caution is urged when attributing CAD to trivial trauma until further research is conducted.

Systematic reviews of observational studies, however, remain a contentious issue.^{26,66} Identification of potential forms of bias is especially important in observational studies, which are particularly sensitive to information- and selection-bias, and confounding. No study was found to be deficient in all 3 areas in this review; however, several studies were deficient in 2. This applied to the studies of connective tissue disease,^{3,4} homocysteine,⁴² infection,^{12,13} migraine,^{13,31,46} manipulation of the neck,⁴⁴ and vessel abnormalities.^{29,40} Of the remaining studies, conflicting results were found for α_1 -AT.^{12,14,38} The methodologically stronger study by Konrad et

‡References 3, 4, 9, 10, 12–14, 27–31, 37, 38, 40, 44, 46, 47

al³⁸ suggested that proteinase inhibitor levels are not important in CAD. Additionally, 2 studies of homocysteine based their results on a rather small sample size,^{9,10} as did the studies of vessel abnormalities^{28,30,45} (cases, range: N=25 to 32). The remaining study of homocysteine has the lowest risk of biased results.³⁷ Finally, whereas the gene association/gene mutation studies generally scored poorly, we accept the possibility that these types of studies may not lend themselves to a rigid methodological criteria as we have used here.

Implications for Research

Future studies should use a multi-factorial design, healthy age- and sex-matched controls, and should examine other potential triggers in persons genetically predisposed to dissection.

Key Points

(1) A systematic review was conducted which examined risk factors for CAD. (2) Thirty-one publications were examined, which examined risk factors classified into the following categories: genetic or inborn predisposition, environmental factors, trivial trauma, and risk factors for atherosclerosis. (3) Many studies were subject to two important forms of bias common to case-control studies (ie. information-, and selection-bias, and confounding); therefore, their results should be interpreted with caution. (4) One study of homocysteine, which found a weak association with CAD, has the lowest risk of biased results. (5) There is a strong association for risk factors with a genetic component and for trivial trauma, while there is only a weak association for environmental factors.

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