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Neurology 2003;60;1424-1428

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CME

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Abstract—*Objective:* To determine whether spinal manipulative therapy (SMT) is an independent risk factor for cervical artery dissection. *Methods:* Using a nested case-control design, the authors reviewed all patients under age 60 with cervical arterial dissection (n = 151) and ischemic stroke or TIA from between 1995 and 2000 at two academic stroke centers. Controls (n = 306) were selected to match cases by sex and within age strata. Cases and controls were solicited by mail, and respondents were interviewed using a structured questionnaire. The medical records of interviewed patients were reviewed by two blinded neurologists to confirm that the patient had stroke or TIA and to determine whether there was evidence of arterial dissection. *Results:* After interview and blinded chart review, 51 patients with dissection (mean age 41 ± 10 years; 59% female) and 100 control patients (44 ± 9 years; 58% female) were studied. In univariate analysis, patients with dissection were more likely to have had SMT within 30 days (14% vs 3%, $p = 0.032$), to have had neck or head pain preceding stroke or TIA (76% vs 40%, $p < 0.001$), and to be current consumers of alcohol (76% vs 57%, $p = 0.021$). In multivariate analysis, vertebral artery dissections were independently associated with SMT within 30 days (OR 6.62, 95% CI 1.4 to 30) and pain before stroke/TIA (OR 3.76, 95% CI 1.3 to 11). *Conclusions:* This case-controlled study of the influence of SMT and cervical arterial dissection shows that SMT is independently associated with vertebral arterial dissection, even after controlling for neck pain. Patients undergoing SMT should be consented for risk of stroke or vascular injury from the procedure. A significant increase in neck pain following spinal manipulative therapy warrants immediate medical evaluation.

NEUROLOGY 2003;60:1424–1428

Approximately 16 to 19% of strokes in young patients are attributed to spontaneous cervical arterial dissection,[1,2] often accompanied by neck or head pain. The true incidence is unknown as dissections do not always produce neurologic signs but has been estimated at 2.6 per 100,000.[3]

The majority of spontaneous dissections are idiopathic, but certain uncommon conditions predispose to dissection, including fibromuscular dysplasia,[4,5] Ehlers-Danlos syndrome type IV,[6] a novel type-I collagen gene mutation in a single case,[7] and cystic medial necrosis.[8] Although significant cranio-

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Received October 1, 2002. Accepted in final form January 31, 2003.

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cerebral trauma can cause dissection, it remains unclear whether minor trauma or simple self-initiated head and neck motions can produce dissection. Several reports of single and groups of cases have described incidents of cervical arterial dissection after spinal manipulative therapy (SMT).[9-13] However, from these uncontrolled studies, it is unclear whether patients with spontaneous cervical arterial dissection seek SMT because of neck pain or whether SMT either causes dissection or exacerbates a preexisting dissection leading to stroke.

We designed a nested case-control study to determine whether SMT is associated with dissection among young patients with stroke or TIA, and to evaluate other potential risk factors for dissection.

Methods. The combined databases of two academic stroke centers (University of California, San Francisco and Stanford Medical Center) were searched for all patients evaluated for ischemic stroke or TIA from 1995 through 2000 who were aged 60 years or less at the time of the event. From this cohort of 1,107 patients, a total of 151 dissection cases were identified, and 306 with other identified causes of stroke were randomly selected as controls, with matching by sex and within 10-year age strata. The study design was approved by local institutional review boards.

Patients were solicited by mail and follow-up phone call for participation in the study. Two investigators (M.W. and P.A.) administered a standardized questionnaire by telephone (n = 185) or in person (n = 3) without knowledge of the patient's diagnosis. The hospital records of all interviewed patients were reviewed independently by two neurologists (S.C.J. and D.R.G.) blinded to questionnaire results and database diagnosis to determine if the patient had clinical and radiographic evidence of ischemic stroke or TIA. Based on the clinical history and imaging data, the neurologist reviewers also classified strokes as small vessel or not small vessel[14] and determined whether the vascular event was caused by an arterial dissection. In order to be classified as dissection, the patient was required to have at least one laboratory confirmation of dissection. For strokes ascribed to causes other than dissection, the relevant etiology was classified as cardioembolic, carotid atherosclerosis, intracranial atherosclerosis, large vessel thrombotic, small vessel thrombotic, embolus of unknown etiology, and other. Disagreements were resolved by a third, blinded reviewer (W.S.S.).

Patient demographics and medical history were obtained by questionnaire and chart review. The results of diagnostic studies were abstracted from hospital records. Statistical analysis was performed with Stata, version 6.0 (Stata Corporation, College Station, TX). Significance of proportions was tested with Fisher exact test, and the Wilcoxon rank sum test was used for continuous variables. In multivariate analysis, all variables associated with dissection in univariate analysis ($p \leq 0.20$) were included in a logistic regression model, and variables no longer contributing ($p > 0.05$) were removed in a stepwise manner.

Results. A total of 457 patients met enrollment criteria and were solicited by mail and follow-up telephone call. A total of 188 patients (72 dissection patients and 116 controls) consented to interview; 256 patients were unable to be contacted and 13 patients declined consent to participate. Thirty-seven patients were excluded after record review—leaving 51 dissection and 100 control patients—for the following reasons: lack of complete medical records (n = 9), iatrogenic dissection with or without stroke (n = 8), severe trauma (n = 1), diagnosis was not stroke or TIA (n = 7), age greater than 60 years (n = 2), arterial dissection without stroke or TIA (n = 10). Of the initial 72 cases classified as dissection in the two hospital databases, all cases were classified as dissection after blinded record review except for two, in which medical records were incomplete.

Patients were matched for sex (table 1), but despite matching by 10-year age strata, patients with dissections tended to be 3.4 years younger. The two groups had several significant differences in the number and type of diagnostic studies performed, likely reflecting the clinical method of determining cause for stroke or TIA. Strokes caused by dissection were more likely to be large vessel (85%) than were nondissection strokes (56%, $p < 0.001$). In univariate analysis, patients with dissection were less likely to have coronary disease, and were more likely to be current consumers of alcohol (table 2). Fibromuscular dysplasia was present only in dissection cases. Although there was no difference in smoking status and number of pack-years of smoking between groups, there was a marked difference in exposure to cigarettes among smokers; smokers with dissections had 7.23 ± 8.26 (SD) pack-years compared with smokers in the control group of 21.8 ± 23.3 pack-years ($p = 0.005$). No connective tissue disorders were identified in patients or family members. Family history of stroke/TIA, family history of fibromuscular dysplasia, and family history of thrombophilia were not different between the groups. Recreational drug use during life was common and similar between groups. The presence of illness within 30 days of stroke or TIA was not different between groups.

Patients with cervical arterial dissection were more likely to report head and neck pain (table 3) both during and before the stroke. Information about location, duration, and quality of neck and head pain was incomplete due to limited patient recall. There was no difference between groups in time of onset of this pain relative to stroke or TIA. Twenty-seven percent of patients with

Table 1 *Demographics, diagnostic procedures, and stroke/TIA etiology*

Characteristics	Dissection, n = 51	Controls, n = 100	*p* Value*
Age, y, mean (SD)	40.6 (10.1)	44.0 (9.1)	0.052
Female, n (%)	30 (59)	58 (58)	0.99
Stroke, n (%)	46 (90)	95 (95)	0.31
TIA, n (%)	5 (10)	5 (5)	
Diagnostic procedures, n (%)			
Conventional angiogram	27 (53)	35 (35)	0.038
MRI brain	43 (84)	79 (79)	0.52
MRA intracranial	19 (37)	46 (46)	0.39
MRA neck	34 (67)	31 (31)	<0.001
Duplex ultrasound	8 (16)	29 (29)	0.08
MRI neck fat sat	9 (18)	5 (5)	0.017
CTA	1 (2)	3 (3)	0.99
Transesophageal echo	9 (18)	39 (39)	0.009
Hypercoagulable tests	7 (14)	41 (41)	0.001
Etiology			
Cardioembolic		20 (20)	
Carotid atherosclerosis		6 (6)	
Intracranial atherosclerosis		8 (8)	
Embolus unknown origin		36 (36)	
Small vessel thrombotic		21 (21)	
Large vessel thrombotic		4 (4)	
Other		5 (5)	
Carotid dissection	26 (51)		
Vertebral dissection	25 (49)		

* Based on Fisher exact test (categorical variables) or Wilcoxon rank-sum test (continuous variables).

MRA = MR angiogram; fat sat = fat saturation technique; CTA = CT angiogram.

Table 2 *Risk factors for cervical artery dissection*

Risk factors	Dissection, n = 51	Controls, n = 100	*p* Value
Hypertension	18 (35)	49 (49)	0.12
Diabetes	2 (4)	15 (15)	0.055
Coronary artery disease	0	9 (9)	0.029
Hypercholesterolemia	18 (35)	42 (42)	0.48
Smoking			
Ever smoked	25 (49)	51 (51)	0.86
Current smoker	8 (16)	18 (18)	0.82
Pack-years, y, mean (SD)	3.4 (6.7)	10.8 (19.7)	0.19
DVT/PE	2 (4)	8 (8)	0.49
Fibromuscular dysplasia	2 (4)	0	0.11
Oral contraceptives			
Ever taken	20 (67)	39 (67)	0.99
Currently taking	2 (7)	1 (2)	0.27
Cocaine, ever used	14 (27)	21 (21)	0.24
Amphetamine, ever used	9 (18)	21 (21)	0.67
Alcohol			
Ever drank	47 (92)	82 (82)	0.14
Current consumer	39 (76)	57 (57)	0.021
Illness within 30 days	22 (43)	30 (30)	0.15

DVT = deep venous thrombosis; PE = pulmonary embolus.

dissection had stroke or TIA within 12 hours of pain onset, 50% within 3 days, and 80% within 1 week.

Those with dissection were more likely to have had SMT within 30 days of the index stroke or TIA (see table 3). Ten patients (three control and seven dissection) were able to provide detailed information about the timing of SMT and timing of pain symptoms relative to the stroke or TIA. The three patients without dissection received SMT on average 8.4 days before the neurovascular event. Two of these three patients experienced no significant change in neck discomfort following SMT, and the other had complete resolution of neck pain. The cause of stroke in these three patients was embolus of unknown origin (all had MRI and MRA of head and neck and transesophageal echocardiography, and one had conventional angiography). The seven patients with dissection received SMT closer to the neurovascular event (1.36 days, $p = 0.011$, Wilcoxon rank sum test). Six of these seven patients (86%) had vertebral artery dissection (one bilateral), in contrast to the cohort of dissection patients in which vertebral dissections represented 25 of 51 cases (49%). Of these 7 patients, 4 (57%) had substantial increase in or new and different pain immediately following SMT and all four had vertebral artery dissections. Two of the dissection patients (28%) had a stroke within seconds of receiving SMT; both patients had vertebral dissections.

Table 3 *Head and neck pain and spinal manipulative therapy (SMT)*

Pain and SMT	Dissection, n = 51	Controls, n = 100	*p* Value
Pain			
Before, during, or after	42 (82)	50 (50)	<0.001
Pain before stroke/TIA	39 (76)	40 (40)	<0.001
Onset before stroke/TIA, d, mean (SD)	7.3 (10.9)	6.3 (9.0)	0.31
SMT			
Ever	27 (53)	42 (42)	0.23
Within 30 d	7 (14)	3 (3)	0.032
New pain or worse pain after SMT	4 (8)	0 (0)	0.012
Immediate stroke/TIA with SMT	2 (4)	0 (0)	0.11
Time from manipulation to stroke/TIA, d, mean (SD)	1.4 (1.2)	8.4 (9.0)	0.011

In multivariate analysis of significant variables from univariate analysis (diabetes, coronary artery disease, current alcohol consumer, illness within 30 days, pain before stroke, and SMT within 30 days), three variables were found to be independently associated with dissection: head or neck pain before stroke/TIA, current alcohol consumption, and recent illness (table 4). These three variables were also independently associated with carotid dissections as a subset. SMT performed within 30 days of stroke/TIA was independently associated with vertebral dissections alone (see table 4), even after adjusting for the complaint of pain before stroke/TIA. These results did not change after controlling for age or restricting the analysis to patients under age 45 years (the age of the oldest patient with dissection who received SMT within 30 days). In univariate analysis, SMT within 30 days was correlated with the complaint of head or neck pain before stroke, with 9 of 79 (11%) with head or neck pain receiving SMT compared with 1 of 71 (1.4%) without head or neck pain ($p = 0.019$). Coronary artery disease was present in all patients with nondissection stroke/TIA and thus was not included in the model. Similarly, fibromuscular dysplasia was only found in patients with dissection and was not used in the model.

Discussion. In this nested case-control study, we compared patients with spontaneous cervical artery dissection to a control group of patients with stroke and TIA of similar age and sex to ascertain what risk factors should alert a physician to consider dissection as the cause of stroke and to better understand the role of SMT in the pathogenesis of dissection. We found a strong relationship between recent SMT and vertebral artery dissection in this study. This association is likely causal for several reasons: 1) there is an independent association between recent SMT and vertebral artery dissection even after controlling for presence of head and neck pain before stroke/TIA, 2) 57% of patients with dissections who later had a stroke or TIA noted a remarkable increase in their head or neck pain with SMT whereas none of the control patients reported this phenomenon, 3) two patients with vertebral artery dissection had stroke within seconds of neck manipulation, 4) the latency from SMT to neurovascular event was shorter for patients with dissections, and 5) six of seven dissections closely related to SMT were of the vertebral artery.

The association between SMT and vertebral artery dissection has been reported previously in several case reports and case series[9-13,15-18] but outside of the frequently reported close temporal relationship between manipulation and stroke, it has not been possible to establish causation. Patients may have an arterial dissection directly from SMT, or patients may seek SMT because of pain produced by a preexisting, spontaneous dissection. If SMT was

Table 4 *Multivariate analysis*

	All dissections, n = 51		Vertebral dissections, n = 25		Carotid dissections, n = 26	
Variable	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Pain before stroke/TIA	4.6 (2.1–10)	<0.001	3.8 (1.3–11)	0.012	4.7 (1.7–13)	0.003
SMT within 30 d	NS		6.6 (1.4–30)	0.015	NS	
Illness within 30 d	2.3 (1.0–5.1)	0.042	NS		3.8 (1.4–10)	0.009
Alcohol, current	2.7 (1.1–6.2)	0.023	NS		3.9 (1.2–13)	0.021

prompted by pain from a dissection, it could still contribute to the risk of stroke or TIA by either extending the dissection or dislodging an embolus, or SMT could have no effect at all on the risk of dissection or stroke or TIA.

Several case reports of immediate onset neurologic symptoms in patients without pre-existing neck pain, as we observed in one case here, suggest that SMT can directly produce dissection. It is highly improbable that a young patient will have a stroke and have had SMT within seconds purely by chance given the relatively low frequency of both events. The selective vulnerability of the vertebral artery to mechanical dissection is likely due to its horizontal course along the atlas where it can be compressed or placed under traction as the head is extended and rotated.[13,18] The initial mural hemorrhage may be produced by shearing of the vasa vasorum by distraction of the artery from the surrounding fascia in which these nutrient arteries arise.[16]

It is more difficult to establish a causal relationship for patients who develop neck pain and then seek SMT for relief of pain. A Canadian study based on national health records found that patients with stroke caused by arterial dissection were fivefold more likely to have recently visited a chiropractor.[11] Because pain is a consistent feature of arterial dissection (76% found here), patients may have sought SMT for the neck pain produced by a spontaneous dissection. In our study, the use of SMT was highly correlated with the complaint of head and neck pain, but despite this colinearity, recent SMT was found to be an independent risk factor for vertebral artery dissection after controlling for pain. Additionally, of those patients in our study who had pain before SMT, more than half of those with dissections had significant worsening in pain with SMT, and the latency to the neurovascular event was shorter than in those without dissection. These findings suggest that SMT may exacerbate pre-existing dissections. This is confirmed by one case report in the literature providing pathologic evidence that SMT can exacerbate dissection.[17] A patient who died of a stroke developed neck pain 18 days before and had SMT with worsened neck pain 15 days before death. Histologic analysis of the vertebral artery revealed mural hemorrhage of two distinct ages correlating with the onset of neck pain and the date of SMT. From this case report and our study, it appears that SMT may exacerbate pre-existing dissections, producing immediate or delayed embolization. It is important, then, to avoid SMT in patients with spontaneous dissections. However, aside from having stroke or TIA symptoms, there appear to be no clear distinguishing features of dissection-related neck pain and pain of musculoskeletal origin to alert the therapist to this entity.[10] Nevertheless, if SMT is performed and the patient either experiences neurologic signs or symptoms, or experiences marked increase or new neck pain, prompt referral for neurologic evaluation is warranted. Patients should be screened for symptoms of pre-existing dissection such as TIA before SMT. Additionally, because SMT is a medical procedure, it seems that practitioners should consent patients for the possibility that neck manipulation can cause stroke or TIA.

Although several cases of dissection reported here appeared to be caused or worsened by SMT, the majority of dissections remain unexplained. Patients with cervical arterial dissection tended to be healthier than patients with stroke and TIA of other cause. In our univariate analysis, patients without traditional risk factors for atherosclerosis were at risk for dissection, confirming results found elsewhere.[19] Fibromuscular dysplasia was found only among patients with dissection, but no other vascular factors correlated with presence of dissection, including connective tissue disorders. We found a similar prevalence of recent illness in our patients to those reported elsewhere,[19] and this was associated independently with carotid artery dissections in our study. This implicates a potential infectious etiology, but despite detailed investigation no specific cause has been identified.[19] We found a significantly higher prevalence of current alcohol consumption in patients with dissection, an association that, to our knowledge, has not been previously reported. Determining whether this association is robust will require further study.

This study has several limitations. The data were collected retrospectively from a population of patients who responded to solicitation. Those with dissection who had undergone SMT may have been more likely to participate if they were motivated to disclose the perceived cause of their stroke or TIA. However, the hypothesis about SMT was not revealed in the solicitation letter, and only 13 patients with dissection who were reached refused to partici-

pate in the study, so selection probably did not substantially bias our results. Further, recall bias cannot be ruled out; patients who had dissection may have been more likely to remember undergoing SMT and to report it on survey several years later, particularly if physicians had suggested it may have caused the dissection. Finally, diagnostic workup was not standardized and some patients classified as nondissection may have had an undetected dissection. Bias may have been introduced if physicians were motivated by the history of SMT to rule out dissection. Although a prospective study could reduce the potential for selection bias and recall bias, and could standardize diagnostic workup, it may be difficult to obtain a large enough sample given the rarity of the disease.

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