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Background and Purpose—Chronic infectious diseases may increase the risk of stroke. We investigated whether periodontal disease, including periodontitis and gingivitis, is a risk factor for cerebral ischemia.

Methods—We performed a case-control study with 303 patients examined within 7 days after acute ischemic stroke or transient ischemic attack, 300 population controls, and 168 hospital controls with nonvascular and noninflammatory neurological diseases. All subjects received a complete clinical and radiographic dental examination. The individual mean clinical attachment loss measured at 4 sites per tooth served as the main indicator for periodontitis.

Results—Patients had higher clinical attachment loss than population ($P<0.001$) and hospital ($P=0.010$) controls. After adjustment for age, sex, number of teeth, vascular risk factors and diseases, childhood and adult socioeconomic conditions, and lifestyle factors, the risk of cerebral ischemia increased with more severe periodontitis. Subjects with severe periodontitis (mean clinical attachment loss >6 mm) had a 4.3-times-higher (95% confidence interval, 1.85 to 10.2) risk of cerebral ischemia than subjects with mild or without periodontitis (≤3 mm). Severe periodontitis was a risk factor in men but not women and in younger (<60 years) but not older subjects. Periodontitis increased the risk of cerebral ischemia caused by large-artery atherosclerosis, cardioembolism, and cryptogenic etiology. Gingivitis and severe radiologic bone loss were also independently associated with the risk of cerebral ischemia, whereas caries was not.

Conclusions—Our study indicates that periodontal disease, a treatable condition, is an independent risk factor for cerebral ischemia in men and younger subjects. **(*Stroke*. 2004;35:496-501.)**

Key Words: infection ■ inflammation ■ risk factors ■ stroke

The established risk factors do not fully account for the risk of stroke.[1] Recently, chronic infectious diseases, including periodontal disease, were also linked to stroke risk. Gingivitis and periodontitis are among the most common human infections. Gingivitis can develop within days and includes inflammatory changes of the gingiva most commonly induced by accumulation of dental plaque. Periodontitis results from a complex interplay between chronic bacterial infection and the inflammatory host response, leading to irreversible destruction of tooth-supporting tissues, with tooth loss as a common end point.[2] Periodontitis is associated with elevated markers of inflammation[3] that are themselves indicators of stroke risk. Bacteria from periodontal pockets can enter the bloodstream during activities such as chewing or tooth brushing,[4] and periodontal pathogens were identified in carotid plaques,[5] but their role in atherogenesis is not yet understood.

Seven studies have investigated the association between stroke and periodontal disease and/or tooth loss: 2 small case-control studies[6,7] and 5 cohort studies, of which 2 relied on self-reported periodontal disease[8,9] and 3 represented posthoc analyses.[10–12] Five of these studies found significant associations between stroke and periodontal disease.[6,7,9,10,12] Evidence on the role of periodontal disease in stroke is still limited because of small sample size, retrospective data analyses, or potential residual confounding. We performed a case-control study, including a complete clinical and radiographic examination of oral hard and soft tissues, to investigate whether periodontal disease is independently associated with acute ischemic stroke or transient ischemic attack in general and with its etiologic subtypes.

Subjects and Methods

We investigated 303 hospitalized patients with acute cerebral ischemia from one university hospital, 300 population controls, and 168 hospital controls. Subjects had to be native German speakers between 18 and 75 years of age living in a defined area around the university hospital. Exclusion criteria included pregnancy, inability to give informed consent or to cooperate in the dental examination within 1 week after ischemia (patients) or admission (hospital

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TABLE 1. Demographic Variables and Risk Factors

Variable	Patients With Cerebral Ischemia	Population Controls	Hospital Controls	*P*	
				Patients vs Population Controls	Patients vs Hospital Controls
Age, y	59.7±11.2	59.3±8.0	55.3±11.5	0.60	<0.001
Female sex, n (%)	95 (31.4)	87 (29.0)	79 (47.0)	0.53	<0.001
Hypertension, n (%)	172 (56.8)	102 (34.0)	49 (29.2)	<0.001	<0.001
Smoking, n (%)				<0.001	0.04
Never	98 (32.3)	150 (50.0)	66 (39.3)		
Ex-smoker*	95 (31.4)	87 (29.0)	50 (29.8)		
Current	110 (36.3)	63 (21.0)	52 (31.0)		
Pack-years (lifetime)	28.9±23.3	27.9±25.1	20.2±14.5	0.07	0.01
Diabetes mellitus, n (%)	71 (23.4)	21 (7.0)	20 (11.9)	<0.001	0.03
Hyperlipidemia, n (%)	109 (36.0)	90 (30.0)	51 (30.4)	0.08	0.32
Previous stroke/transient ischemic attack, n (%)	86 (28.4)	10 (3.3)	5 (3.0)	<0.001	<0.001
Coronary heart disease, n (%)	46 (15.2)	19 (6.3)	13 (7.7)	0.002	0.20
Peripheral arterial disease, n (%)	34 (11.2)	8 (2.7)	6 (3.6)	<0.001	0.06
Atrial fibrillation, n (%)	21 (6.9)	4 (1.3)	2 (1.2)	0.007	0.05
Alcohol drinking,† n (%)				0.002	0.02
No or low	110 (36.3)	90 (30.0)	79 (47.0)		
Moderate	171 (56.4)	202 (67.3)	87 (51.8)		
Heavy	22 (7.3)	8 (2.7)	2 (1.2)		
Family history of stroke,‡ n (%)	110 (36.3)	88 (29.3)	39 (23.2)	0.02	0.01
School education ≥10 y, n (%)	89 (29.4)	118 (39.3)	63 (37.5)	0.003	0.14
Current or last profession, n (%)				0.003	0.19
Homemaker	17 (5.6)	12 (4.0)	8 (4.8)		
Untrained	21 (6.9)	5 (1.7)	10 (6.0)		
Blue collar	116 (38.3)	109 (36.3)	67 (39.9)		
White collar	112 (37.0)	122 (40.7)	64 (38.1)		
Academic	30 (9.9)	44 (14.7)	16 (9.5)		
Father's profession, n (%)				0.008	0.08
Untrained	7 (2.3)	2 (0.7)	2 (1.2)		
Blue collar	215 (71.0)	188 (62.7)	109 (64.9)		
White collar	52 (17.2)	72 (24.0)	37 (22.0)		
Academic	13 (4.3)	27 (9.0)	12 (7.1)		

Nutritional factors (meat, sugar, vitamin C, vitamin E, beta-carotene),[15] mother's profession, availability of fixed hot water during childhood,[16] and body mass index were not different between groups ($P>0.1$; data not shown). Probability values are based on univariate logistic regression analysis stratified for sex and age.

*Nonsmoker for at least 2 years.

†No or low, 0 to 25 L pure alcohol/lifetime; moderate, 25 to 1000 L pure alcohol/lifetime; heavy, >1000 L pure alcohol/lifetime.

‡First-degree relative with stroke.

controls), and known conditions requiring prophylactic antibiotic treatment before dental examination.

Patients with acute cerebral ischemia had ischemic stroke (acute ischemic lesion on brain imaging and/or neurological deficits lasting >24 hours; n=208) or transient ischemic attack (neurological deficit of <24 hours without new ischemic lesions; n=95). Cerebral hemorrhages were excluded by neuroimaging in all patients. Among 497 consecutive patients (August 1998 through January 2000), 367 were eligible, and 303 (82.8%) agreed to participate. Patients were examined within 3.3±2.2 days (mean±SD) after ischemia. We used established criteria for etiologic stroke subtype analysis[13] (atherothrombosis: atherosclerotic stenosis ≥50% in ipsilateral brain-supplying artery without alternative etiology; cardioembolism: high- or medium-risk source of cardiac embolism[13] without alternative etiology; microangiopathy: presence of 1 of 5 lacunar syndromes and infarction <1.5 cm of diameter without alternative etiology; cryptogenic: absence of stroke etiology despite complete workup).

We received a 2% random sample of all inhabitants 18 to 75 years of age from the official population registry of the study area. Population controls were randomly selected from this sample, frequency matched to patients by age and sex, and examined parallel to patient recruitment. Among 497 controls contacted, 435 were eligible, and 300 (69.0%) participated. Hospital controls were selected from patients consecutively hospitalized at the neurology

TABLE 2. Intraoral Variables Among the 3 Groups

Variable	Patients With Cerebral Ischemia	Population Controls	Hospital Controls	*P* Patients vs Population Controls	*P* Patients vs Hospital Controls
Tooth brushing ≤1 time daily, n (%)	82 (32.9)	95 (33.6)	27 (18.2)	0.66	0.06
<1 Dental visits per year, n (%)	80 (31.6)	40 (14.1)	23 (15.5)	<0.001	0.005
Teeth,* n	15.14±9.43	19.19±8.30	17.71±9.0	<0.001	0.33
Decayed teeth, n	1.0±1.57	0.74±1.35	0.63±1.15	0.061	0.058
Filled teeth, n	9.67±5.41	11.87±5.28	10.31±5.11	<0.001	0.80
DMFT Index	22.10±5.71	20.73±5.72	20.43±6.27	0.088	0.21
Gingival index	0.97±0.35	0.68±0.37	0.73±0.37	<0.001	<0.001
Plaque index	1.68±0.60	1.55±0.51	1.39±0.50	0.0012	<0.001
Radiological bone loss, mm	3.82±1.97	3.28±1.53	3.25±1.73	<0.001	0.058
CAL, mm	4.30±1.33	3.87±1.18	3.78±1.33	<0.001	0.001

Data include only subjects with at least 1 tooth except for number of teeth and DMFT Index. Probability values are based on univariate logistic regression analysis stratified for sex and age.

*Including wisdom teeth.

and neurosurgery departments of the same hospital and investigated parallel to patients with ischemia. Subjects with vascular, inflammatory, or alcohol or drug-derived neurological diseases or with brain metastases were excluded. Among 259 eligible patients, 168 (64.9%) participated. Patients had diseases of the vertebral column (n=89), primary central nervous system tumors (n=54), and neurodegenerative (n=14) and other neurological (n=11) diseases. All participating individuals gave informed consent for study participation and separately for radiography. The study protocol was approved by the local ethics committee.

Interview and Dental Examination

Trained interviewers used a standardized questionnaire that focused on previous diseases and vascular and periodontal risk factors, including a detailed assessment of smoking and drinking habits,[14] nutrition,[15] childhood and adult social history,[16] past and present medication use, and dental care (eg, frequency and duration of tooth brushing, frequency of dentist visits, previous dental treatments). Risk factors—eg, hypertension and diabetes mellitus—were diagnosed if the patient reported that a physician had previously diagnosed the condition or if the patient was on treatment. All individuals were examined in a standardized way in a dental unit under optimum conditions with illumination by a standard dental light, compressed air, and a mouth mirror. Dental examinations were performed by a trained dentist (C.K.; 89.6%) or by a calibrated substitute (R.L.; 10.4%). Radiographs were analyzed in a blinded manner (all by R.L.).

For assessment of periodontitis, the clinical attachment loss (CAL; distance between probed base of the pocket and cementoenamel junction) was selected as the primary variable. Measurements were performed in all teeth at 4 sites to the nearest millimeter with a North Carolina periodontal probe.[17] Individual mean values were calculated. Attachment levels were analyzed as a continuous variable and after stratification into absence of periodontitis or mild periodontitis (defined as mean CAL ≤3 mm) and steps of 1.5 mm (mean CAL, 3 to 4.5, 4.5 to 6, and >6 mm), with mean CAL >6 mm defined as severe periodontitis. Gingivitis severity was assessed with the Löe and Silness Gingival Index that is based on gingival bleeding after skimming a periodontal probe 1 mm into the crevicular sulcus to irritate the gingiva. Higher index numbers represent more severe gingivitis. Severe gingivitis was defined as index values >1.2. Dental plaque was graded according to the Silness and Löe Plaque Index.[18] Plaque and gingivitis were scored at 4 sites per tooth (buccal, mesiolingual, lingual, and distolingual) and averaged for each subject. At least 1 remaining tooth was required for these analyses. For assessment of caries, teeth were slightly air dried and visually inspected with a dental mirror. Only teeth with visible cavitation were taken as decayed. The number of decayed (D), missing (M), and restored teeth (FT) was calculated according to the DMFT Index system.[19] Panoramic radiographs were taken in 261 stroke cases (86%), 152 hospital controls (89%), and 285 population controls (95%). Radiographic bone loss was measured as the distance from the cementoenamel junction to the most apical extension of the bony defect at 2 sites per tooth (mesial and distal), expressed as absolute values (in millimeters) and relative to the overall root length (in percent), and averaged in each individual.

Statistical Analysis

Conditional logistic regression analysis stratified by age (5-year age groups) and sex, as described recently,[20] was used to analyze the association of factors with cerebral ischemia. All factors of interest were first analyzed separately and adjusted for number of teeth in dental parameters. In the multivariate model, the CAL was included, plus those factors considered important a priori (hypertension, diabetes mellitus, smoking, alcohol consumption, atrial fibrillation, previous cerebral ischemia, other ischemic vascular diseases, family history of stroke, school education, profession) or significant ($P<0.05$) in univariate analysis. Individuals with no teeth left (≥28 teeth missing) were assigned an additional category. Subgroup analyses by number of teeth were also performed. Linear tests for trend were performed with scored variables. Odds ratios (ORs) and 95% confidence intervals (CIs) are given for all factors. Both control groups were combined in multivariate analyses on the basis of mostly similar results in univariate analysis of dental variables.[21] The SAS software package PROC PHREG was used for the analyses.

Results

Tables 1 and 2 depict demographic data, risk factors, and results from dental examinations. The mean CAL was higher, indicating more severe periodontitis, in patients than in both control groups. Similar results were found for number of teeth, gingivitis, radiological bone loss, and plaque index (Table 2). After adjustment for age, sex, number of teeth, and other covariables, increasing severity of periodontitis was associated with an increasing risk of cerebral ischemia. Severe periodontitis increased the risk by a factor of 4.3 (Table 3). In contrast, missing teeth, plaque index, and caries were not independent risk factors. Similar results were

TABLE 3. ORs for Clinical Attachment Loss and Other Risk Factors*

Variable	OR	95% CI	*P*
Dentist visits <1 time/y	2.19	1.41–3.4	<0.001
Clinical attachment level,† mm			
≤3	1.0		
3–≤4.5	1.40	0.81–2.4	0.23
4.5–≤6	2.74	1.41–5.3	0.003
>6	4.34	1.85–10.2	<0.001
Plaque index†			
≤1	1.0		
1–≤1.5	0.36	0.04–3.2	0.35
1.5–≤2	1.76	0.30–10.4	0.53
>2	0.41	0.06–2.9	0.37
Missing teeth			
0	1.0		
1–19	0.97	0.42–2.2	0.95
20–27	0.75	0.27–2.05	0.57
All	1.50	0.52–4.44	0.46
≥1 Tooth with caries†	0.88	0.59–1.3	0.53
Hypertension	1.81	1.24–2.6	0.002
Diabetes mellitus	2.25	1.35–3.8	0.002
Smoking‡	1.48	1.10–2.0	0.001
Ex-smoker	0.69	0.44–1.07	0.098
High lifetime alcohol consumption§	3.16	1.26–7.92	0.014
Atrial fibrillation	7.13	2.42–21.0	<0.001
Coronary heart disease and/or peripheral arterial disease	1.47	0.87–2.5	0.15
Previous stroke or transient ischemic attack	9.87	5.23–18.6	<0.001
Family history of stroke	1.58	1.08–2.33	0.020
School education ≥10 y	1.25	0.79–2.0	0.34
Current or last profession‖	0.86	0.70–1.07	0.18
Father's profession‖	0.68	0.49–0.95	0.020

*All variables simultaneously in 1 model stratified by sex and age.

†Individuals without teeth in separate category.

‡Variable entered as continuous covariable, log-transformed [log (pack-years+1)]; OR for 10 vs 0 pack-years.

§Lifetime consumption of >1000 L pure alcohol, approximately corresponding to 1.5 L beer per day over 40 years.

‖Score 0 (low) to 4 (high) (see Table 1); the OR given relates to a difference of 1.

obtained when patients with first-ever stroke or transient ischemic attack were analyzed separately (Table 4). Periodontitis represented a risk factor in men and younger subjects but not in women or older individuals (>60 years). Regarding etiologic subgroups, severe periodontitis was an independent risk factor for atherothrombotic, cryptogenic, and cardioembolic origins (Table 4). Subgroup analyses by number of teeth showed an increased risk by severe periodontitis in subjects with <10 teeth missing (OR, 9.02; 95% CI, 1.03 to 79.4; model as in Table 3) but not in those with 10 to 27 teeth missing (OR, 1.47; 95% CI, 0.39 to 5.6). In subjects with >5 remaining teeth, severe periodontitis was still associated with increased risk (OR, 6.7; 95% CI, 2.39 to 19.0).

In multivariate analysis, severe radiological bone loss and severity of gingivitis were significantly associated with cerebral ischemia. Similar results were found if patients with transient ischemic attack were excluded from the analyses (Table 5). Severity of gingivitis was not correlated with the time period between ischemia and dental examination (R=0.037; P=NS). When gingivitis is added to the multivariate model in Table 4, the role of severe periodontitis is attenuated (OR, 2.09; 95% CI, 0.84 to 5.2), whereas severe gingivitis remains an independent risk factor (OR, 7.27; 95% CI, 2.94 to 18.0).

Discussion

Our results support the hypothesis that periodontal disease is an independent stroke risk factor. This is the first case-control study that performed a meticulous clinical and radiographic evaluation of orodental conditions and etiologic subgroup analyses of stroke as a heterogeneous disease. Our patient group is representative of stroke patients in the age segment studied because our hospital is the main stroke center in the area and stroke patients <75 years of age are commonly admitted to our wards. The role of periodontal disease as a risk factor could be explained by residual confounding, mainly by smoking, a health-neglecting lifestyle, and socioeconomic variables. We separately evaluated every smoking period using a standardized approach[14] and adjusted for adult and childhood socioeconomic variables and specific periodontal risk factors, such as dental plaque and frequency of dentist visits, that are indicators of dental care and general health awareness. These factors did not modify the role of periodontitis. Furthermore, caries that also results from oral neglect was not an independent risk factor. This result is similar to that in a previous study[7] and supports the hypothesis of a specific link between periodontal disease and stroke risk. Nevertheless, a causal relationship cannot be inferred from our data, and large intervention studies are required to test for causality.

Limitations of our study include a possible selection bias toward controls with higher health awareness, although the participation rate in our control groups was comparably good. For obvious reasons, the examiner could not be blinded to patient status, potentially leading to an ascertainment bias. However, radiologic assessment was blinded, and its results confirmed clinical periodontal findings. Stroke patients are older and more often male than other neurological inpatients. This limited age and sex matching with hospital controls, but all comparisons were adjusted for age and sex, allowing full comparability. We had to restrict our study to patients with transient ischemic attack and mild to moderately severe stroke. Therefore, results cannot be transferred to severe and fatal stroke. Residual confounding by factors not adjusted for in the multivariate analysis (eg, physical activity) may be a further limitation.

Periodontitis was an independent risk factor only in younger patients and men. This may be caused by a decreasing role of periodontitis as a risk factor in increasing age and by differences in health awareness between sexes. Periodon-

TABLE 4. ORs for Clinical Attachment Loss in Subgroups*

		OR by Clinical Attachment Loss				
Subgroup	n	≤3 mm	3–≤4.5 mm	4.5–≤6 mm	>6 mm	*P* for Trend
Transient ischemic attack	95	1	1.62 (0.74–3.6)	3.01 (1.17–7.8)	5.91 (1.78–19.7)	0.002
Stroke	208	1	1.48 (0.77–2.8)	3.16 (1.52–6.6)	3.38 (1.35–8.4)	<0.001
First-ever stroke	150	1	1.28 (0.66–2.5)	2.17 (1.01–4.7)	2.82 (1.10–7.2)	0.008
Women	95	1	1.28 (0.56–2.9)	1.74 (0.58–5.3)	1.57 (0.29–8.6)	0.35
Men	208	1	1.58 (0.77–3.2)	3.42 (1.52–7.7)	4.94 (1.87–13.1)	<0.001
Age ≤60 y	144	1	1.81 (0.92–3.5)	3.43 (1.39–8.5)	6.13 (1.62–23.2)	0.001
Age >60 y	159	1	0.86 (0.35–2.2)	1.71 (0.65–4.5)	1.78 (0.60–5.3)	0.055
Etiology of cerebral ischemia†						
Cardioembolism	70	1	1.74 (0.72–4.2)	3.48 (1.22–9.9)	2.35 (0.47–11.8)	0.038
Atherothrombosis	85	1	1.17 (0.44–3.1)	2.65 (0.92–7.6)	3.32 (1.00–11.0)	0.006
Microangiopathy	50	1	1.02 (0.28–3.8)	2.42 (0.59–9.9)	3.19 (0.55–18.4)	0.067
Cryptogenic	53	1	2.77 (0.89–8.7)	8.50 (2.30–31.3)	13.2 (2.68–64.7)	<0.001

*Adjusted for hypertension, diabetes mellitus, smoking (pack-years), previous stroke, father's profession, dentist visits, and number of teeth, stratified by sex and age.

†Twenty patients had other defined causes. In 25 patients, cause of stroke remained unclear, but not all investigations required were performed.

titis was associated with cerebral ischemia caused by large-artery atherosclerosis, supporting the hypothesis of a possible link between periodontitis and atherogenesis or complications of atherosclerosis.[5] There was also a strong association with cryptogenic stroke and, to a lesser degree, with cardioembolism. Active periodontal inflammation may contribute to a prothrombotic state via recurrent bacteremia, platelet activation, and elevated clotting factors, thereby increasing the risk of cardioembolism and cryptogenic stroke.[22]

Two lines of evidence further support the hypothesis that active periodontal inflammation increases stroke risk. First, edentulousness in which periodontal inflammation is usually absent was not an independent risk factor; in contrast, severe periodontitis was a more important risk factor in those with several teeth left. Second, gingivitis was strongly and independently associated with cerebral ischemia. When tested together with periodontitis, severe gingivitis even appeared as the more important risk factor. Gingivitis is an indicator for the actual status of periodontal inflammation. As shown recently, acute infection is a trigger for ischemic stroke.[23] Bone loss and attachment loss require longer periods to develop[2] and therefore undoubtedly preceded cerebral ischemia. Because of its fast development, gingivitis could partly be a sequel of poor health care after stroke. However, we rapidly examined our patients and found no correlation between gingivitis and time elapsed after ischemia. This may support the hypothesis that gingivitis preceded cerebral ischemia. Gingivitis was not a significant risk factor for stroke in a recent cohort study,[12] a finding that is not surprising given the discontinuous presence and variable strength of the disease over time. Periodontal disease is a chronic inflammatory disease with acute exacerbations and periods of quiescence, and periodontal conditions at the time of acute ischemia may be of major interest.

TABLE 5. ORs for Radiographic Bone Loss and Gingivitis*

Variable				
Mean radiographic bone loss, mm	≤2.5	2.6–4.0	4.1–5.5	>5.5
All subjects				
OR (95% CI)	1	0.95 (0.59–1.54)	1.29 (0.70–2.35)	2.76 (1.25–6.06)
Stroke patients only†				
OR (95% CI)	1	0.81 (0.48–1.39)	0.93 (0.47–1.85)	2.45 (1.09–5.51)
Gingival index	≤0.4	0.5–0.8	0.9–1.2	>1.2
All subjects				
OR (95% CI)	1	1.62 (0.83–3.16)	4.30 (2.29–8.06)	9.01 (3.78–21.46)
Stroke patients only†				
OR (95% CI)	1	1.70 (0.74–3.92)	5.02 (2.30–11.0)	10.07 (3.70–27.4)

*Covariables as in Table 4.

†Patients with transient ischemic attack excluded.

In conclusion, our study indicates that periodontal disease is significantly associated with cerebral ischemia. Gingivitis and periodontitis are treatable and preventable conditions. Therefore, their identification as stroke risk factors that require further studies would have a major impact on stroke prevention.

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