Association of Periodontal Diseases with Intracranial Aneurysm Formation: Novel Predictive Indicators

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Abstract

Background and purpose: We investigated whether periodontal diseases, specifically, periodontitis and gingivitis, could be risk factors of the incidence of intracranial aneurysms (IAs).

Methods: We performed a case–control study to compare the differences in the periodontal disease parameters of 281 cases that were divided into the IA and non-IA groups. All cases underwent complete radiographic examination for IAs and examination for periodontal health.

Results: Compared with those in the non-IA group, the cases in the IA group were older (53.95 ± 8.56 vs 47.79 ± 12.33, $p < 0.001$) and had a higher incidence of hypertension (76 vs 34, $p = 0.006$). Univariate analysis revealed that age (>50 years) and hypertension were risk factors of aneurysm formation (odds ratio [OR] 1.047, 95% confidence interval [95%CI] 1.022–1.073, $p < 0.001$ and OR 2.047, 95%CI 1.232–3.401, $p = 0.006$). In addition, univariate and multivariate logistic regression analyses showed that the parameters of periodontal diseases, including gingival index, plaque index, clinical attachment loss, and alveolar bone loss, were significantly associated with the occurrence of IA (all $p < 0.05$). For further statistical investigation, the parameters of periodontal diseases were divided into four layers on the basis of their averages. Poor periodontal health condition was correlated with a high risk of IAs.

Conclusion: Periodontal diseases, especially severe gingivitis or periodontitis combined with hypertension, were significantly associated with the incidence of IAs.

Introduction

Intracranial aneurysms (IAs) are pathological dilatations of cerebral arteries; they are most often saccular in shape and frequently found in proximal cerebral artery bifurcations[1]. Subarachnoid hemorrhages caused by IA rupture are rare events that affect 10–11/100,000 population per year in Western populations[2]. IA rupture and subsequent hemorrhage may account for a mortality rate of 35%, and most survivors of IAs are left with considerable neurological impairment[3–4]. Unruptured IAs are commonly treated through endovascular intervention or neurosurgical procedures to decrease the possibility of subarachnoid hemorrhage. However, most unruptured IAs are asymptomatic, and patients ignore potential risks. Thus, IAs must be screened before rupture, and the pathological mechanism of aneurysm formation should be emphasized.

Periodontitis and gingivitis are chronic inflammatory responses of the oral supporting tissues (gingiva, periodontal ligaments, and alveolar bone) surrounding the teeth[5–7]. Periodontitis results from the complex interplay between chronic bacterial infection and inflammatory host response and leads to the irreversible destruction of tooth-supporting tissues with tooth loss as a common end point[8]. Gingivitis develops gradually and includes inflammatory changes in the gingiva that are most commonly induced by the accumulation of dental plaque. In recent years, researchers have investigated the association between systematic vascular diseases and periodontitis or gingivitis. Lockhart et al. reported that oral

bacterial deoxyribonucleic acid (DNA) has been found in arteries and suggested that oral infections may contribute to vascular wall inflammation[9]. Bacteria from periodontal pockets and their secreta, such as endotoxins, have been identified in cardiovascular atherosclerotic lesions[10–12]. Iwai investigated the potential role of periodontal diseases in the pathobiology of abdominal aortic aneurysms[13]. He detected periodontal bacterial DNA in abdominal aortic aneurysmal walls and then concluded that poor periodontal conditions have important effects on the progression of abdominal aortic aneurysms.

Nine studies have found significant associations between periodontal diseases and cerebravascular strokes[14–22]. Further clinical studies speculated that periodontal inflammation caused by Streptococcus mutans participates in the occurrence of intracranial hemorrhage strokes[23–25]. However, evidence for the role of periodontal diseases in IAs has received insufficient attention because of the availability of insufficient sample sizes. Therefore, we performed this case–control study to investigate whether periodontal diseases are associated with IA formation and to discover novel epidemiological evidence.

Method

Study population

From September 2015 to September 2018, we collected cases that were admitted to our institution for IA detection via digital subtraction angiography or computer tomography angiography examination. During the same period, we also recruited cases that were diagnosed without IAs or several volunteers. A total of 281 cases provided written informed consent and were divided into two groups (166 cases in the IA group and 115 cases in the non-IA group). The privacy of the patients was strictly protected, and the protocol of this study was approved by our ethics committee. We subjected all recruited cases to periodontal health examination through a standardized approach in a dental unit by using a standard dental light, compressed air, a mouth mirror, and digital panoramic radiography free of charge. Periodontal disease was diagnosed on the basis of the clinical and radiographic criteria described by the 1999 Consensus Classification of Periodontal Diseases[26].

Inclusion criteria were as follows: (1) individuals who were 18–80 years of age, (2) individuals with IAs and hospitalized volunteers (non-IA) who wanted to participate in this study, and (3) individuals who underwent the examination of periodontal health condition. Exclusion criteria included (1) individuals with acute ruptured aneurysms; (2) individuals receiving antihypertensive therapy with calcium channel blockers, such as Nifedipin; (3) individuals with severe cardiovascular diseases or cerebral ischemic stroke; (4) individuals with malignant diseases, chronic inflammatory diseases, or antibiotic use within 2 weeks; and (5) individuals missing clinical follow-up. Baseline demographic information (including age, sex, clinical presentation, smoking and drinking history, diabetes, hypertension, and hypercholesterolemia) and IA characteristics (location, size, shape, and quantity) were recorded.

Assessment of periodontal diseases

Periodontal diseases mainly include periodontitis and gingivitis. Gingivitis severity was assessed by using the gingival index (GI) system, which is based on the various tendencies of gingival bleeding after gingival irritation. A high index number (> 1.1) was defined as severe gingivitis. Periodontitis was evaluated by using the plaque index (PI), clinical attachment loss (CAL), and alveolar bone loss (ABL). Plaque and gingivitis were scored at four sites per tooth (buccal, mesiolingual, lingual, and distolingual) and averaged for each subject. We presented these parameters in accordance with the following definitions: First, the CAL was examined by inserting the tip of a CPI probe to measure the distance between the pocket and cementoenamel junction. Attachment levels were analyzed as continuous variables, and mean CAL > 4 mm was considered as severe periodontitis. Second, dental plaque was scored in accordance with the PI system, which is based on the same principle as the GI system. We divided PI into 4 sites (≤ 0.5, 0.51–1.0, 1.01–1.5, and > 1.5). A high score represented severe periodontitis. Third, ABL levels were measured as the distance from the cementoenamel junction to the most apical extension of the bony defect. We stratified the ABL into < 3, 3.00–4.00, 4.00–5.00, and > 5.00 mm. Among these periodontal parameters, the CAL was defined as the primary criterion of periodontitis.

Statistical analysis

Data were presented as mean ± standard deviation or expressed in terms of frequencies and percentages. Independent sample t-tests and chi-square tests were performed to test for differences in continuous or categorical variables between the IA group and the non-IA group, respectively. Subgroup univariate and multivariate logistic regression analyses were performed to identify the independent contribution of gingivitis and periodontitis parameters (including GI, CAL, PI, and ABL) to the incidence of IAs. Odds ratios (ORs) and 95% confidence intervals (CIs) were given for all periodontal parameters. A two-sided p value of < 0.05 was considered to be significant. Statistical analysis was performed by using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA).

Results

A total of 281 cases (including 174 [61.9%] females and 107 [38.1%] males) were recruited in this study. The ages of these cases ranged from 18 years to 79 years (51.34 ± 10.56 years). Table 1 shows the baseline characteristics and subgroup analysis results of the IA and non-IA group. No statistically significant differences were detected in the distributions of sex, diabetes mellitus, hyperlipidemia, cerebrovascular history (including cerebral ischemic and hemorrhage events), other personal history (such as alcohol, smoking, and BMI) in the two subgroups (all p > 0.05). Chi-square tests indicated that cases in the IA group were older than those in the non-IA group (53.95 ± 8.56 vs 47.79 ± 12.33, p < 0.001) and had a higher incidence of hypertension (76 vs 34, p = 0.006).

Table 1
Baseline Characteristics of Patients

Variable	IA(+), n = 166	IA(-), n = 115	P-value
Age	53.95 ± 8.56	47.79 ± 12.33	< 0.001
Sex, M:F	67:99	40:75	0.383
Hypertension	76	34	0.006
Diabetes mellitus	11	15	0.093
Hyperlipidemia	17	9	0.537
Ischemic stroke	6	7	0.392
Intracerebral hemorrhage	4	1	0.652
Smoking	36	18	0.222
Drinking	19	20	0.165
Family history	21	9	0.241
BMI	25.18 ± 4.25	24.46 ± 3.77	0.145
Data are shown as mean ± SD or absolute and Chi-square test between 2 groups;			
M: male; F: female; BMI: Body Mass Index			

Table 2 provides the parameters of gingivitis and periodontitis. Significant statistical differences were found in GI, PI, CAL, and ABL (all $p < 0.001$) between the IA and non-IA group. IA cases had higher GI, PI, CAL, and ABL than non-IA cases. Univariate regression analysis revealed that these parameters, combined with age (over 50 years) and hypertension, were significantly associated with the occurrence of IAs (all $p < 0.05$) (Table 3).

Table 2
The differences of periodontitis parameters between IA group and non-IA group

Variable	IA(+), n = 166	IA(-), n = 115	P-value
GI	0.79 ± 0.38	0.49 ± 0.28	< 0.001
PI	1.06 ± 0.69	0.68 ± 0.40	< 0.001
CAL	3.33 ± 0.75	2.99 ± 0.73	< 0.001
ABL	3.47 ± 1.05	2.79 ± 0.79	< 0.001
Data are shown as mean ± SD or absolute and Chi-square test between 2 groups;			
IA: intracranial aneurysm; non-IA: non-intracranial aneurysm;			
GI: gingival index; PI: plaque index; CAL: clinical attachment loss;			
ABL: alveolar bone loss;			

Table 3
Univariate analysis of clinical characteristics and periodontitis parameters for intracranial aneurysm formation

Variables	univariate regression analysis			
	P-value	OR	95% CI	
Age(≥50 years)	< 0.001	1.047	1.022	1.073
Hypertension	0.006	2.047	1.232	3.401
GI	< 0.001	11.428	5.318	24.557
PI	< 0.001	3.053	1.908	4.885
CAL	0.001	1.794	1.252	2.571
ABL	< 0.001	2.211	1.613	3.030
OR: Odds Ratio; 95% CI: 95% Confidence Interval;				
GI: gingival index; PI: plaque index; CAL: clinical attachment loss;				
ABL: alveolar bone loss;				

The parameters of periodontal diseases (GI, CAL, PI, and ABL) were divided into four layers on the basis of their averages and referenced literature[27]. Table 4 demonstrates that severe periodontitis and gingivitis might be accompanied by the high risk of IA formation. GI could be considered as a risk factor of IAs (OR of GI > 1.1, 17.11; 95%CI 3.339–87.66). High PI (mainly > 1.5) showed a similar association (OR 6.968, 95%CI 2.396–20.259). High CAL (> 4.00 mm), which indicated periodontitis with increased severity, was accompanied by the high risk of IA (OR 4.074, 95%CI 1.012–16.391). The severity of ABL (>

4.00 mm) represented another significant risk factor of IAs with two OR values, specifically, 4.00–5.00 mm, which corresponded to an OR of 6.409, and over 5.0 mm, which corresponded to an OR of 21.835. The values of 95% CI are shown in Table 4. All of the above parameters of severe periodontal diseases had $p < 0.05$.

Table 4
Association Between Periodontal Disease and Intracranial Aneurysm

Variable		P-value	OR	95% CI	
				Lower limit	Upper limit
Gingival index	< 0.3 [a]				
	0.3–0.7	0.128	0.553	0.258	1.185
	0.71–1.1	0.114	2.034	0.844	4.905
	> 1.1	0.001	17.110	3.339	87.660
Plaque index	≤ 0.5 [b]				
	0.51-1.0	0.294	0.687	0.341	1.384
	1.01–1.5	0.726	0.852	0.349	2.084
	> 1.5	< 0.001	6.968	2.396	20.259
Clinical attachment loss	< 3 mm [c]				
	3.00-3.50 mm	0.997	1.001	0.509	1.970
	3.50-4.00 mm	0.067	0.433	0.176	1.061
	> 4.00 mm	0.048	4.074	1.012	16.391
Alveolar bone loss	< 3 mm [d]				
	3.00–4.00 mm	0.260	1.410	0.775	2.564
	4.00–5.00 mm	0.003	6.409	1.907	21.533
	> 5.00 mm	0.005	21.835	2.503	190.463

Adjusted with age, hypertension. OR: Odds Ratio; 95% CI: 95% Confidence Interval;

[a] "<0.3" used as reference group in the binary logistic regression.

[b] "≤0.5" used as reference group in the binary logistic regression.

[c] "<3mm" used as reference group in the binary logistic regression.

[d] "<3mm" used as reference group in the binary logistic regression.

Discussion

Periodontitis and gingivitis are associated with the risk of several diseases, such as rheumatoid arthritis and atherosclerosis[28–29]. Recent studies have discussed the role of periodontal diseases in causing cerebral ischemia. Chiu demonstrated that periodontitis is associated with stroke caused by large-artery atherosclerosis; this result supports the hypothesis of a possible link between periodontitis and atherosclerosis[30]. After adjusting for confounding vascular factors on the basis of etiologic subgroup analysis, Grau et al. concluded that severe periodontitis is an independent risk factor for IA with atherothrombotic origins (OR 2.35 [1.00–11.0] and OR 13.2 [2.68–64.7]) and that gingivitis is independently associated with cerebral ischemia given its value as an indicator of the actual status of periodontal inflammation[31]. These findings suggest that chronic periodontal inflammatory responses contribute to a prothrombotic state via recurrent bacteremia and platelet and endothelial activation. Plaque destabilization is a potential trigger of cardioembolism and cryptogenic stroke[32–33]. In addition, the accumulation of oxidized lipids in vascular walls and subsequent atherosclerotic remodeling may be altered indirectly by systemic immunization induced by local periodontitis.

Periodontal diseases, especially periodontitis, are associated with the remodeling of the aneurysmal wall in abdominal aortic aneurysms. In experimental models, periodontal bacteria promote the degeneration of the abdominal aortic aneurysmal wall by increasing the recruitment of neutrophils to the intraluminal thrombus that covers the inner portion of the abdominal aortic aneurysm[34]. The pathologies of IA and abdominal aortic aneurysm share several features[35]. The current understanding is that IAs form as the end result of flow-driven inflammatory cell-mediated cerebral artery wall remodeling at sites where high flow exerts high wall shear stress[1]. However, IA is not detected in all cases under high flow and shear stress in the bifurcations of cerebral arteries. Previous studies on the association between periodontal diseases and stroke focused on the pathological mechanism of IA. Pyysalo is the first to detect the presence of oral bacteria DNA in ruptured and unruptured intracranial aneurysmal walls[36]. Hallikainen et al. speculated that periodontitis predisposes the artery wall toward aneurysm development[37]. However, few works have focused on the relationship between intracranial hemorrhagic diseases and periodontal diseases. In this case–control study, we focused on the potential association between periodontal diseases (including periodontitis and gingivitis) and IAs. Although GI, PI, CAL, and ABL have long been known as actual indicators of periodontal inflammation caused by multitudinous oral bacteria, we were the first to demonstrate that these parameters were independent risk factors of IAs ($p < 0.05$, Table 3). Further subgroup analysis demonstrated that poor periodontitis parameters might be associated with the high incidence of IA. A past observation demonstrated that systemic elastase activity may play an important role given that increased serum elastase concentrations are associated with IAs, although the source of serum elastase is unknown[38]. Potential sources for circulating elastase are macrophages or neutrophils[39]. Tooth brushing or chewing disseminates periodontal Porphyromonas gingivalis (PG), especially in patients with periodontitis or gingivitis, to extraoral sites via circulation and then induces systemic inflammatory responses through transient bacteremia[40]. PG can modify dendritic cell function and induce proinflammatory cytokine production in macrophages. Thus, periodontal pathogens that

infiltrate cerebral arteries likely lead to excessive collagen degradation and neutrophil accumulation in the thrombus, promoting changes in the course of cerebral artery remodeling[41]. In another mechanism, neutrophils induced by periodontal pathogens are a major source of proteolytic activity because they release the matrix metalloproteinases MMP-8 and MMP-9, myeloperoxidase, and elastase and then accelerate the course of proteolytic or cytotoxic injury[42]. The ultimate pathology is damage to the elastic fibers of smooth muscles and the degeneration or necrosis of the intima medium. In combination with chronic hypertension, external vascular walls swell to form IAs.

Previous literature has indicated that age (especially over 50 years) and hypertension are predictive risk factors of IA formation[43–44]. In the present study, we included patients who were older than 50 years or suffered hypertension and found that these cases had an increased incidence of IAs. Systemic hypertension not only affects tissue remodeling or vascular wall inflammation by exerting abnormal hemodynamic stresses but also activates the local renin–angiotensin system[45]. Moreover, hypertension may mediate vascular inflammation through the activation of NF-kappa B, which can further promote inflammation[46]. The continuous stimulatory response caused by hypertension and inflammation can result in the degeneration of vascular walls and then induce IA formation.

This study has several limitations. First, although the literature has indicated that periodontal treatment can induce bacteria to transfer to systematic circulation, we could not persuade all patients to undergo periodontal or caries treatment because of their poor obedience. Thus, we will further study whether periodontal treatment has low relevance to IA. Second, the specific values of periodontal disease parameters that have the optimal predictive values for the incidence of IAs should be quantified through receiver operating characteristic curve analysis. Third, we did not perform further experimental research on inflammatory mediators that might cause IA directly. Fourth, other studies have demonstrated that age and hypertension are associated with the high risk of periodontal diseases. In this study, we only attempted to investigate the mechanism of aneurysm formation and neglected the relationship between these two factors and periodontal diseases.

Conclusion

Periodontal diseases were significantly associated with the high incidence of IA. Given our results, patients with severe gingivitis or periodontitis with hypertension should be encouraged to undergo cerebrovascular examination. Mechanistic experiments on inflammatory response will positively affect the risk prediction of IA.

List Of Abbreviations

ABL: alveolar bone loss

BMI: body mass index

CTA: computer tomography angiography

CAL: clinical attachment loss

CIs: confidence intervals

DNA: deoxyribonucleic acid

DSA: digital subtraction angiography

IA: intracranial aneurysm

GI: gingival index

MMP: matrix metalloproteinases

OR: Odds ratios

PI: plaque index

PG: porphyromonas gingivalis

SAH: subarachnoid hemorrhage

Declarations

Ethics approval:

Institutional review board approval was obtained from Beijing Tiantan Hospital's ethics committee for this study.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Contributorship Statement:

Author contributions to the study and manuscript preparation include the following.

Youxiang Li and Huijian Ge conceived the study design.

Keyun Liu and Jia Sun completed the collection and collation of the original data.

Keyun Liu, Jia Sun, Huijian Ge filtered the final data according to the criteria.

Keyun Liu and Lingling Shao analyzed and sorted out the data.

Keyun Liu and Huijian Ge drafted and wrote the manuscript.

Youxiang Li and Huijian Ge supervised the project, obtained the research grants, made key revisions and final approvals to the manuscript.

All authors made substantial contributions to the manuscript, read and approved the final version of manuscript.

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