Is Periodontitis a Risk Factor for Cognitive Impairment and Dementia? A Case-Control Study

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Background: Dementia is a multi-etiologic syndrome characterized by multiple cognitive deficits but not always by the presence of cognitive impairment. Cognitive impairment is associated with multiple non-modifiable risk factors but few modifiable factors. Epidemiologic studies have shown an association between periodontitis, a potentially modifiable risk factor, and cognitive impairment. The objective of this study is to determine whether clinical periodontitis is associated with the diagnosis of cognitive impairment/dementia after controlling for known risk factors, including age, sex, and education level.

Methods: A case-control study was conducted in Granada, Spain, in two groups of dentate individuals aged >50 years: 1) cases with a firm diagnosis of mild cognitive impairment or dementia of any type or severity and 2) controls with no subjective memory loss complaints and a score >30 in the Phototest cognitive test (screening test for cognitive impairment). Periodontitis was evaluated by measuring tooth loss, plaque and bleeding indexes, probing depths, and clinical attachment loss (AL).

Results: The study included 409 dentate adults, 180 with cognitive impairment and 229 without. A moderate and statistically significant association was observed between AL and cognitive impairment after controlling for age, sex, education level, oral hygiene habits, and hyperlipidemia ($P = 0.049$). No significant association was found between tooth loss and cognitive impairment.

Conclusion: Periodontitis appears to be associated with cognitive impairment after controlling for confounders such as age, sex, and education level. *J Periodontol 2015;86:244-253.*

KEY WORDS

Dementia; mild cognitive impairment; periodontal attachment loss; periodontitis.

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Dementia is a multi-etiologic syndrome characterized by the acquired involvement of multiple cognitive/behavioral domains that compromise the sufferer's functional capacity.[1] It primarily affects the elderly, although it can commence at any age.[1] Mild cognitive impairment is an intermediate state, appearing frequently before the development of dementia, in which the cognitive and behavioral impairment is not sufficiently severe to have functional repercussions.[2] The main cause of dementia is Alzheimer disease (AD), a neurodegenerative process of multifactorial and complex etiology associated with multiple risk and protective factors; its prevalence increases exponentially with age from 65 years on, and it represents one of the main socio-health problems faced by the developed world.[3] It is estimated that there will be 35.6 million individuals with dementia worldwide in 2010 and that this number will double every 20 years, reaching >115 million by 2050.[1] The magnitude of the challenge and the absence of curative treatments make the development of preventive measures a matter of extreme urgency. Although many risk factors are non-modifiable (e.g., age, sex, and genetic risk factors), others are susceptible to modification through individual choices, e.g., certain dietary and lifestyle factors, or through medical intervention, as in the case of

doi: 10.1902/jop.2014.140340

hypertension and diabetes, among other relevant diseases.[4,5]

Inflammation, blood vessel damage, and oxidative stress play an important role in the etiopathogeny of AD,[6] leading to the hypothesis that periodontitis may be associated with cognitive impairment and dementia.[7] Periodontitis is a local infectious/inflammatory process with potential systemic effects, and the mechanisms mediated by periodontopathogenic microorganisms and the inflammation they activate may explain the initial vascular damage and repercussions at both the cardiovascular[8] and cerebral[9] levels. There is increasing evidence that periodontitis may be a modifiable risk factor for cardiovascular disease,[10-13] but its association with dementia or cognitive impairment is less clear. Some studies using samples from wide epidemiologic surveys have reported associations between oral health status and cognitive function,[14] between the presence of antibodies against periodontopathogens and some cognitive functions,[15,16] and between increased cognitive impairment and greater tooth loss.[17,18] Other authors have reported an association of cognitive decline or AD with the presence of ε allele 4 of the apolipoprotein E gene,[19] an increase in tumor necrosis factor-α (TNF-α), and the presence of antibodies against periodontopathogens.[20] In a recent postmortem analysis, Poole et al.[21] detected lipopolysaccharide from *Porphyromonas gingivalis* in cerebral tissue from patients with AD, suggesting the possible role of inflammation of dental origin in the etiopathogeny of this disease.

The hypothesis of the present study is that periodontal disease is associated with dementia and/or mild cognitive impairment. The study objective is to determine whether clinical periodontitis is associated with the diagnosis of cognitive impairment/dementia after adjustment for known risk factors, such as age, sex, oral hygiene habits, and education level.

MATERIALS AND METHODS

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)[22] Statement recommendations were followed in the design and reporting of this study.

Design, Site, and Sample Size

This case-control study was conducted in Granada, Spain, between January 2011 and December 2012. Cases were recruited from the Neurology Departments of two hospitals (Virgen de las Nieves University Hospital and San Cecilio University Hospital, Granada, Spain), and controls were recruited from among non-dental patients treated in a primary care center (La Caleta, Granada, Spain). The sample size was calculated to detect a 20% difference in the prevalence of moderate or severe clinical attachment loss (AL; i.e., patients with ≥33% of sites with >3 mm of AL) between cases and controls, with 80% power and 5% α error, yielding a total sample size of 182 per group (1:1 ratio). However, the final effective sample size was larger (n = 409) and the case-to-control ratio was slightly altered (180 cases to 229 controls) after application of the study eligibility criteria. Sample selection consisted of 160 males and 249 females, aged 51 to 98 years old; mean ages were: 77.0 years in cases and 78.5 years in controls. All participants gave their written informed consent to participate in the study, which was approved by the ethics committee of the University of Granada.

Sample selection. All cases were selected from among patients treated in a behavioral and cognitive neurology department, who were assessed by a neurologist expert in dementia (CC-P, JM, or RV) with a guided anamnesis, general/neurologic examination, and extensive neuropsychologic assessment, using a standard battery of tests that included orientation, attention, language, verbal/visual memory, executive capacity, and praxis. All patients also underwent behavioral (neuropsychiatric inventory scale[23]) and functional (Barthel index,[24] Lawton and Brodie scale[25]) assessment and global staging (global deterioration scale[26] and clinical dementia rating scale[27]). The study was completed with the complementary examinations recommended by the Spanish Society of Neurology, including an analytical study (blood count, general biochemistry, thyroid hormones, vitamin B12, folic acid, and lues serology) and structural neuroimaging (cranial computed tomography or brain magnetic resonance imaging). The diagnosis criteria adopted were from the Diagnostic and Statistical Manual of Mental Disorders-IV for dementia, from the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association[28] for AD and from the Spanish Society of Neurology Behavioral and Dementia Study Group for cognitive impairment.[29]

Controls were recruited from among individuals visiting the primary healthcare center for reasons other than a dental or neurologic problem. Before their enrollment, they were clinically assessed with a guided anamnesis and general examination and underwent the Phototest, a brief cognitive test designed to screen for cognitive impairment/dementia in the primary health care setting.[30] This test has been validated in the Spanish population, does not require pen or paper for its completion, is not influenced by education level, and can be applied in illiterate individuals (who comprise an appreciable proportion of this elderly population). The Phototest has also demonstrated greater effectiveness at

a lower cost compared with the Mini-Mental State Examination in the present authors' setting.[31]

For both study groups (cases and controls), the inclusion criteria were as follows: 1) be dentate and 2) aged >50 years. The exclusion criteria were as follows: 1) the presence of depressive illness, schizophrenia, or personality disorder; 2) acute or chronic disease not under medical treatment; 3) consumption of drugs of abuse; and 4) receipt of periodontal treatment in the previous 6 months. An additional inclusion criterion for the cases group was a firm diagnosis of mild cognitive impairment or dementia of any type or severity, and additional inclusion criteria for the control group were the absence of subjective memory complaints and a Phototest score of >30 points.[30]

Clinical examination. The neurologic examination of the cases was performed by one neurologist in each hospital, applying the above-reported diagnostic criteria. Data were also gathered on the following: 1) age; 2) sex; 3) education level; 4) tobacco and alcohol consumption; 5) hyperlipidemia; 6) hyperglycemia; and 7) family, personal, medical, and pharmacologic histories related to cognitive impairment, i.e., potential confounders. After the neurologic examination, cases were classified as having mild cognitive deficit without dementia or mild, moderate, or severe dementia according to the abovementioned criteria.

A complete clinical oral examination was performed by four dentists (IS-L and three collaborators). The present study focuses on four clinical variables: 1) plaque index (PI); 2) bleeding index (BI); 3) AL; and 4) probing depth (PD). The intraexaminer and interexaminer (versus dentist with experience in epidemiologic studies [JAG-M]) agreement was tested before the study, repeating the examination in eight to 10 patients per dentist and calculating the intraclass correlation coefficient (ICC) for the study variables. The ICC was adequate, ranging from 0.63 to 0.93 depending on the variable, dentist, and type (interexaminer or intraexaminer).[32] The periodontal examination was performed with the patient in seated position, using a mirror and periodontal probe.¶ The following variables were recorded: 1) total number of teeth present (including third molars); 2) Löe and Silness index;[33] 3) AL (sum of PD and distance between the cemento-enamel junction and the gingival margin); 4) PD (from the gingival margin to the base of the periodontal pocket); and 5) bleeding on probing (BOP).[34] The number of teeth lost was considered a proxy of periodontal disease. At least three sites were examined in at least two teeth per sextant or in all teeth when <12 were present. The degree of periodontitis was defined[35] by the percentage of sites with AL >3 mm as follows: 0% = absent; 0% to 32% = mild; 33% to 66% = moderate; and 67% to 100% = severe. Data were also gathered on the patients' oral hygiene habits and visits to the dentist.

Statistical Analyses

A statistical package# was used for the data analyses, applying the tests indicated in the table footnotes. After descriptive and comparative analyses of the study variables, multiple logistic regression analysis was applied, considering the number of teeth present (as proxy variable) and the AL, adjusting the analysis for known potential confounders and for oral hygiene habits.

RESULTS

The study finally included 409 dentate adults, 180 with cognitive impairment (cases) and 229 without (controls). The main reason for non-participation was a lack of time. The mean age of cases and controls was 77.0 and 78.5 years, respectively; 67.2% of cases and 55.9% of controls were female (Table 1). Of the 180 cases, 21 had mild cognitive impairment (without dementia), 123 mild or moderate dementia, and 36 severe dementia; 70% of the patients with dementia were diagnosed with AD. No significant differences were found between cases and controls in age, education level, or consumption of alcohol or tobacco. A significant association was observed between hyperlipidemia and membership in the case group (odds ratio [OR] = 1.92; P = 0.004). Participants whose sole oral hygiene habit was a mouthwash had a 11.37-fold higher risk of cognitive impairment compared with those who brushed their teeth twice or more a day (95% confidence interval [CI] = 5.46 to 23.68; P <0.001).

In general, the oral health status of the cases was worse than that of the controls. The risk of cognitive impairment was 1.76-fold greater in participants with fewer teeth and 15.7-fold greater in those with higher versus lower PIs (Table 2). No or only mild periodontal disease was diagnosed in 10% of the cases, moderate periodontitis in 21.7%, and severe periodontitis in 68.3%, with significant differences versus controls. BOP, PD, and AL were significantly associated with the diagnosis of cognitive impairment in the bivariate analyses (Table 2). The risk of cognitive impairment was more than three-fold higher in patients with severe periodontitis versus those with no or mild periodontitis; OR = 3.04; 95% CI = 1.69 to 5.46).

Table 3 exhibits the associations found between the periodontal variables studied and the different degrees of cognitive impairment/dementia. The variables requiring a prolonged period to appear

¶ UNC periodontal probe, Hu-Friedy, Chicago, IL.
# SPSS v.15.0, IBM, Chicago, IL.

Table 1.

Bivariate Association Between Cognitive Impairment (cases) and Studied Variables (N = 409)

Variable	Controls (n = 229)	Cases (n = 180)	Crude OR (95% CI)	*P*
Age (years), mean ± SD	78.5 ± 7.9	77.0 ± 7.8		0.06*
Age (years), n (%)				0.18†
51 to 69	33 (14.4)	24 (13.3)	1.00	
70 to 79	94 (41.0)	87 (48.3)	1.27 (0.70 to 2.32)	
80 to 89	82 (35.8)	62 (34.4)	1.04 (0.56 to 1.93)	
90 to 98	20 (8.7)	7 (3.9)	0.48 (0.18 to 1.32)	
Sex, n (%)				0.03‡
Male	101 (44.1)	59 (32.8)	1.00	
Female	128 (55.9)	121 (67.2)	1.62 (1.08 to 2.43)	
Education level, n (%)				0.35†
High (n = 22) or secondary (n = 20)	28 (12.2)	14 (7.9)	1.00	
Primary	51 (22.3)	35 (19.7)	1.37 (0.63 to 2.97)	
Primary incomplete	104 (45.4)	85 (47.8)	1.63 (0.81 to 3.30)	
None	46 (20.1)	44 (24.7)	1.91 (0.89 to 4.10)	
Missing	—	2		
Tobacco, n (%)				0.11‡
No	206 (90.0)	165 (94.8)	1.00	
<20 (n = 25) or ≥20 (n = 7) cigarettes/day	23 (10.0)	9 (5.2)	0.49 (0.22 to 1.08)	
Missing	—	6		
Alcohol, n (%)				0.81†
No	195 (85.2)	146 (83.4)	1.00	
1 to 6 times/week	24 (10.5)	19 (10.9)	1.06 (0.56 to 2.00)	
≥1 times/day	10 (4.4)	10 (5.7)	1.34 (0.54 to 3.29)	
Missing	—	5		
Hyperlipidemia, n (%)				0.004‡
No	154 (75.1)	110 (61.1)	1.00	
Yes	51 (24.9)	70 (38.9)	1.92 (1.24 to 2.97)	
Missing	24	—		
Hyperglycemia, n (%)				0.16‡
No	161 (78.9)	130 (72.2)	1.00	
Yes	43 (21.1)	50 (27.8)	1.44 (0.90 to 2.30)	
Missing	25	—		
Oral hygiene habits, n (%)				<0.001†
≥2 times/day	119 (52.0)	33 (18.3)	1.00	
1 time/day	82 (35.8)	76 (42.2)	3.34 (2.03 to 5.49)	
Only mouthwash	13 (5.7)	41 (22.8)	11.37 (5.46 to 23.68)	
No	15 (6.6)	30 (16.7)	7.21 (3.48 to 14.96)	

OR = odds ratio; CI = confidence interval.
* Student *t* test.
† χ^2 test.
‡ χ^2 test corrected for continuity.

(absence/presence of teeth and AL) showed no significant relationship with the degree of disease, i.e., did not depend on the timing of cognitive impairment onset, with similar periodontal conditions being observed in both early (mild cognitive impairment) and late (severe dementia) stages of the disease. Thus, the most severe stages of periodontal disease were not associated with greater cognitive impairment. These data may indicate that the cause precedes the effect. However, the oral hygiene habits and BI were significantly associated with the gradient of cognitive impairment, observing worse values with greater severity of cognitive impairment/dementia ($P = 0.001$).

Table 2.

Bivariate Association Between Cognitive Impairment (cases) and Dental Variables (N = 409)

Variable	Controls (n = 229)	Cases (n = 180)	Crude OR (95% CI)	*P*
Number of teeth present, mean ± SD	17.4 ± 8.0	15.3 ± 8.0		0.008*
Number of teeth present, n (%)				0.04†
20 to 32	90 (39.3)	63 (35.0)	1.00	
10 to 19	96 (41.9)	64 (35.6)	0.95 (0.61 to 1.50)	
1 to 9	43 (18.8)	53 (29.4)	1.76 (1.05 to 2095)	
Periodontally explored teeth, mean ± SD	14.3 ± 7.2	10.4 ± 5.7		<0.001*
PI, mean ± SD	1.55 ± 0.89	2.37 ± 0.65		<0.001*
PI, n (%)				<0.001†
0.00 to 1.00	75 (32.8)	14 (7.8)	1.00	
1.01 to 2.00	81 (35.4)	29 (16.1)	1.92 (0.94 to 3.90)	
2.01 to 2.50	44 (19.2)	52 (28.9)	6.33 (3.15 to 12.72)	
2.51 to 3.00	29 (12.7)	85 (47.2)	15.70 (7.72 to 31.92)	
BI (%), mean ± SD	50.6 ± 34.2	63.0 ± 31.1		<0.001*
BI (%), n (%)				<0.001*
0.0 to 25.0	62 (27.1)	21 (11.7)	1.00	
25.1 to 50.0	47 (20.5)	37 (20.6)	2.32 (1.21 to 4.48)	
50.1 to 90.0	74 (32.3)	67 (37.2)	2.67 (1.47 to 4.85)	
90.1 to 100	46 (20.1)	55 (30.6)	3.53 (1.88 to 6.63)	
PD (mm), mean ± SD	2.6 ± 1.5	3.0 ± 0.7		<0.001*
AL (mm), mean ± SD	4.5 ± 1.8	4.9 ± 1.6		0.06*
AL (percentage >3 mm), mean ± SD	65.3 ± 35.2	75.0 ± 28.8		0.002*
AL (percentage >3 mm), n (%)				<0.001†
0.0 to 32.9 (absent/mild)	56 (24.5)	18 (10.0)	1.00	
33.0 to 66.9 (moderate)	47 (20.5)	39 (21.7)	2.58 (1.31 to 5.09)	
67.0 to 100 (severe)	126 (55.0)	123 (68.3)	3.04 (1.69 to 5.46)	

* Student *t* test.
† χ^2 test.

Table 4 displays the sequential models for associations of the number of teeth present and AL with cognitive impairment, adjusted for potential confounders and forcing the entry of age and sex, known confounders that also showed significant differences between the groups (Table 1). The significant association of cognitive impairment with the number of teeth present in the bivariate analysis disappeared after adjustment for age, sex, AL, oral hygiene habits, and the presence of hyperlipidemia. However, AL, which develops over years, possibly before the development of dementia symptoms, remained significantly associated with the diagnosis of cognitive impairment with or without dementia after adjustment for the above confounders (replacing AL with the number of teeth present) (Table 4), including oral hygiene habits. The highest risk (OR) was for participants with severe periodontitis versus those with mild or no periodontitis; the consecutive inclusion of potential confounders in the model reduced the ORs, but they remained statistically significant.

DISCUSSION

In this case-control study, a moderate and statistically significant association is observed between AL and cognitive impairment after adjustment for age, sex, education level, oral hygiene habits, and the presence of hyperlipidemia. However, no significant association was found between the number of teeth present and cognitive impairment.

This significant association between periodontitis and cognitive impairment has been demonstrated previously,[14-20] but the direction of this association has yet to be established. Although the present study design prevents the establishment of a cause–effect relation, the nature of this association can be further

Table 3.

Association Between Dental Variables and Levels (gradient) of Cognitive Impairment (n = 180 cases)

Variable	Mild Cognitive Impairment [A] (n = 21)	Mild Dementia [B] (n = 62)	Moderate Dementia [C] (n = 61)	Severe Dementia [D] (n = 36)	Global Comparison *P*	Paired Comparison
Number of present teeth	17.2 ± 7.8	15.5 ± 8.0	15.1 ± 8.1	14.0 ± 7.9	0.53*	—
PI	2.26 ± 0.49	2.27 ± 0.76	2.40 ± 0.57	2.5 ± 0.62	0.18*	—
BI (%)	45.4 ± 20.9	62.0 ± 29.5	61.5 ± 34.2	77.6 ± 27.3	0.001*	A ≠ C; D ≠ A,B,C§
Oral hygiene habits, n (%)					<0.001†	A,B ≠ C,D¶
≥2 times/day	7 (33.3)	16 (25.8)	8 (13.1)	2 (5.6)		
1 time/day	11 (52.4)	29 (46.8)	23 (37.7)	13 (36.1)		
Only mouthwash	3 (14.3)	13 (21.0)	18 (29.5)	7 (19.4)		
No	0 (0.0)	4 (6.5)	12 (19.7)	14 (38.9)		
PD (mm)	2.8 ± 0.5	3.0 ± 0.6	3.1 ± 0.6	3.0 ± 0.9	0.47*	—
AL (mm)	4.6 ± 1.0	4.8 ± 1.4	5.1 ± 2.0	4.7 ± 1.3	0.42*	—
AL (percentage >3 mm)	75.2 ± 19.8	76.6 ± 27.4	73.3 ± 33.8	75.0 ± 27.1	0.94*	—
Severe (67.0% to 100% > 3 mm)	66.7%	67.7%	70.5%	66.7%	0.98‡	—

* Analysis of variance.
† Kruskal-Wallis test.
‡ X^2 test.
§ Student-Newman-Keuls method; ≠ indicates $P<0.05$ for paired comparison.
¶ Mann–Whitney *U* test; ≠ indicates $P<0.05$ for paired comparison.

explored by applying the causality criteria proposed by Bradford Hill,[36] i.e., "strength of association," "consistency," "specificity," "temporality," "biological gradient," "plausibility," "coherence," "experiment," and "analogy." The present results meet the first criterion, strength of association, as shown in Table 4. The criterion of consistency is fulfilled, given the significant association found by numerous authors using varied study designs.[14-17,20,37-39] Secondary analyses of data from national health or nutrition surveys[14,15,37] have also demonstrated an association between poor oral health status and cognitive function, using different exposure measurements, case definitions, and outcome measures, but without including a control group. Most authors[17,19,38] have associated periodontitis and tooth loss with cognitive impairment, offering a moderate quality of scientific evidence, and have concluded that these risk factors preceded the loss of cognitive function, meeting the criterion of temporality. In the present study, this association is strongest with the AL, an indicator of the lifetime experience of periodontal disease, in all patients with cognitive impairment/dementia, independent of its severity (Table 3). Furthermore, AL is a chronic and gradual process, unlike gingival bleeding, that may be influenced by deterioration in the capacity to maintain correct oral hygiene with increasing severity of cognitive disease. In fact, the present results evidence a significant worsening of oral hygiene habits with more advanced cognitive disease. Therefore, it is reasonable to assume that the AL precedes the cognitive impairment, although the lack of association between the other periodontal variables and the level of cognitive impairment may be attributable to the presence of unknown confounders or the reduced number of participants in each subgroup. However, unlike in previous publications,[17,19,38] although a significant difference between the number of teeth present and cognitive impairment was obtained in bivariate analyses, the significance was lost when potential confounders in the logistic regression analysis were controlled for. One explanation may be that, for many years, the only treatment option for caries and/or periodontal disease in the Spanish public health system was tooth extraction, meaning that the number of teeth present/tooth loss may not be a good proxy of periodontal disease in this study population of individuals aged >50 years.

In addition to the acknowledged role of inflammatory processes in these associations, researchers have also implicated the presence of periodontopathic virulence factors,[21] the action of the herpes virus,[40] the copresence of certain phenotypes, and the indirect

Table 4.

Adjusted Associations (OR and 95% CI) of AL and Number of Teeth Present on Cognitive Impairment, by Consecutive Multiple Logistic Regression Models in 409 Individuals

Model*	n†	No. of Teeth Present (REF = 20 to 32)			AL Percentage >3 mm (REF = 0 to 32% [absent/mild])		
		10 to 19	1 to 9	Wald *F* (*P*)	33% to 66% (moderate)	67% to 100% (severe)	Wald *F* (*P*)
1: PT, AL, age, sex	409‡	0.89 (0.56 to 1.43)	1.62 (0.92 to 2.84)	0.10	2.47 (1.23 to 4.96)	2.97 (1.61 to 5.48)	0.002
2: PT, AL, age, sex, studies	407	0.90 (0.55 to 1.46)	1.61 (0.92 to 2.83)	0.11	2.55 (1.26 to 5.16)	2.97 (1.60 to 5.50)	0.003
3: PT, AL, age, sex, studies, OHH	407	0.86 (0.50 to 1.46)	1.39 (0.75 to 2.58)	0.30	2.68 (1.24 to 5.77)	2.30 (1.18 to 4.49)	0.03
4: PT, AL, age, sex, studies, OHH, HL	383	0.76 (0.44 to 1.32)	1.25 (0.67 to 2.36)	0.27	2.64 (1.18 to 5.92)	2.31 (1.15 to 4.66)	0.04

REF = reference category; PT = present teeth; OHH = oral hygiene habits; HL = hyperlipidemia.
* All variables included as indicator dummy variables (for categories of each variable, see Tables 1 and 2).
† Effective sample size after excluding missing values.
‡ For n distribution, see Table 2.

action of periodontal pathogens acting at the vascular level and facilitating atherosclerosis.[41] In general, there is a clear "analogy" with processes in atherosclerotic cardiovascular disease, as noted by some authors.[41] However, regardless of the cause, periodontal disease may represent a source of systemic inflammation.[7] In the present study, in which an association between periodontitis and cognitive impairment has been evidenced, there is no "specificity" of cause, although it has been possible to show a dose–response relationship, supporting the hypothesis that periodontitis may be a risk factor for cognitive impairment. At least in the present population, the risk of cognitive impairment (i.e., being a case) increased with a smaller number of teeth, higher PI, higher BI, or greater percentage of AL.

The available scientific evidence allows the cause–effect relation to be interpreted as having "biologic plausibility" and "coherence." Although not fully clarified, vascular dysfunction[42] and inflammation[43] appear to play a crucial role in the development of dementias in general and AD in particular.[44] The most widely accepted hypothesis is that neurovascular damage is a primary occurrence, and subsequent events, including β-amyloid deposition, exacerbate the vascular damage, leading to neurodegenerative processes and cognitive decline.[43] The role of local/systemic inflammation of periodontal origin in the pathogenesis of AD is also not completely clear, although there is considerable scientific evidence that it may be implicated in the vascular damage. One example is the presence at the systemic level of inflammation factors derived from local inflammation in moderate-to-severe periodontal disease, including interleukin-1β, interleukin-6, TNF-α, and C-reactive protein, among others, which have also been implicated in brain inflammation and subsequent neurodegeneration.[45] An association has also been demonstrated between some serum antibodies to common periodontal organisms and cognitive impairment,[15,16,20] and some interventional studies have reported an improvement in endothelial function after periodontal treatment.[46]

The present case-control study, which includes controls with age and education level similar to those of the cases, provides robust results on the association between the clinical periodontal parameters studied and the presence of cognitive impairment/dementia. Given that periodontitis might possibly be a modifiable risk factor, it would be of major interest to verify these data with interventional studies, both when acute periodontitis is established and in a preventive approach with follow-ups of cohorts ("experimentation").

The main concern in cross-sectional studies is to control for potential confounders, including tobacco use, age, sex, body composition, and history of hyperlipidemia, hypertension, or nutritional deficits,[14] as reported by authors exploring the association between periodontitis and atherosclerotic vascular disease.[41] Multivariate statistical techniques have assisted this process, but there has been no demonstration to date of these associations in populations of non-smokers, individuals without hyperlipidemia, or younger people. In the present study, AL was significantly associated with cognitive impairment after adjusting for some of these confounders, including age, sex, education level, and hyperlipidemia. The possibility was also considered that this association was attributable to the expected worsening of oral hygiene habits with greater cognitive impairment, which would increase the amount of bacterial plaque and debris, producing inflammation and gingival bleeding. However, it is not believed that this effect would have been relevant in relation to the AL, the main clinical finding, because there would have been no impediment to correct oral hygiene during the period of chronic local inflammation in which there would theoretically be systemic involvement (years before the development of cognitive impairment). In fact, deficient oral hygiene was already evidenced during the initial stages of cognitive impairment without dementia, with 67% of participants taking a mouthwash or brushing their teeth only once a day. This conclusion is strengthened by the multivariate analysis results, in which the association remained significant after adjusting for the "oral hygiene habits" variable.

No information was gathered on the history (duration) of tobacco and alcohol use, hypertension, or body composition, and only the presence or absence of hyperlipidemia was recorded, with no quantitative data on lipid levels. An additional limitation of this study is that the examiner was masked to the status of the cases but not to that of the controls, because these had to undertake a cognitive function test (Phototest). Conversely, all examiners were adequately trained and calibrated to reduce the interobserver variability. In the periodontal diagnosis, not all teeth were examined in patients with >12 present, for the convenience of the patients, and it has been suggested that partial-mouth periodontal examinations may underestimate the prevalence and severity of the disease, which may not be evenly distributed in the mouth.[47] Nevertheless, this potential incorrect classification bias is in the direction of the null hypothesis and does not contribute to a Type I error. Finally, the absence of a single and established set of criteria for periodontitis severity means that comparison of the prevalence data with those obtained in other studies should be approached with care. Study strengths are the inclusion of a control group to facilitate the evaluation of possible causal relations and the use of four markers related to different manifestations of periodontal disease, covering the presence and extent of the disease, as recommended by some authors.[48]

Application to the present findings of the causality criteria proposed by Bradford Hill suggests that periodontitis may not only be associated with the presence of cognitive impairment but may also precede it, therefore representing a potentially modifiable risk factor for cognitive decline or dementia. However, additional follow-up studies and clinical trials are required to confirm this hypothesis. In the meantime, special attention should be paid by dentists to the oral hygiene of adults at risk for developing cognitive impairment, with regular examinations and the application of preventive treatments.

CONCLUSION

Periodontitis appears to be associated with cognitive impairment after controlling for age, sex, education level, and oral hygiene habits.

ACKNOWLEDGMENTS

This study was partially funded by Neuron Bio Company. The authors report no conflicts of interest related to this study.

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Submitted June 9, 2014; accepted for publication September 4, 2014.