TITLE: Self-reported periodontitis and migraine. Results from a multicentre, cross-sectional survey in Spain.

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ABSTRACT

The aim of this study was to evaluate self-reported periodontitis (PD) prevalence in migraineurs as well as to investigate the association between both diseases. A cross-sectional survey was carried out including patients diagnosed with migraine attending 12 Spanish Headache Units. We determined diagnosis of PD administering a validated self-reported questionnaire. Socio-demographic, clinical and medical information, co-morbidities, daily habits, migraine characteristics and medication were collected using a questionnaire. Of the 651 consecutive migraineurs included in the study, 393 suffered from chronic migraine (CM). Self-reported PD was detected in 327 patients with migraine (50.2%). Migraineurs with self-reported PD were significantly older and had a previous history of fibromyalgia, stress, anxiety, depression, and allodynia (all $P<0.001$). Additionally, this group of patients consumed more topiramate ($P=0.008$) and simple analgesics ($P<0.001$) than patients with migraine and without self-reported PD. Also they were less active physically and belonged to a low education level (both $P<0.001$). Prevalence of self-reported PD was significantly higher in chronic migraineurs compared to those diagnosed with episodic migraine (EM) (53.9% vs. 44.6%, $P=0.019$). Logistic regression analyses showed that self-reported PD was associated with CM (OR=1.456; 95%CI:1.062-1.997, $P=0.020$). However, after adjusting for significant confounders, the association was attenuated (OR=1.100; 95%CI:0.784-1.543, $P=0.581$). We concluded that self-reported PD was significantly more frequent in CM as compared to EM. Self-reported PD was associated with the presence of CM, although some co-morbidities shared by both diseases could have an effect in this association.

KEY WORDS: periodontitis, headache, prevalence, chronic migraine, epidemiology.

INTRODUCTION

Periodontitis (PD), a chronic gingival infection characterized by periodontal tissue breakdown and bone loss is highly prevalent worldwide. In Spain, it is estimated that 38.4% of the employed adult population has some degree of PD [1]. In the last decade, it has been suggested that PD not only has local effects within the gingiva but also could exert systemic effects [2]. Indeed, it is speculated that the inflamed and ulcerated subgingival pocket epithelium forms an easy port for periodontopathogens to spill into the bloodstream. Furthermore, bacterial components such as lipopolysaccharides may also be disseminated into the blood circulation. These endotoxins together with bacterial antigens can trigger important systemic inflammatory responses. Moreover, pro-inflammatory molecules that are produced within the periodontal tissues may enter into the systemic circulation and exert effects on distant organ systems for instance the brain [2].

In accordance with the survey conducted by the Global Burden of Disease research group, migraine has a global estimated prevalence of 14.7%, which makes this type of neurovascular disorder one of the most common diseases worldwide [3]. Despite the fact that migraine is not a fatal disease, it ranks as the sixth highest cause of disability as measure by years lived with disability (YLDs) [4], being the second leading cause of YLDs in women [3]. Regarding frequency, migraine can be divided into episodic (EM) and chronic migraine (CM). Results from an epidemiological study in a representative random Spanish population showed that almost 5% of the general population suffers from CM [5]. Even though a sterile neurogenic inflammation within the meninges with consequent activation of trigeminal nerve terminals [6], the potent vasodilator effects of the calcitonin gene-related peptide (CGRP) on cranial blood vessels [7] or the idea of cortical spreading depression depolarizing perivascular trigeminal terminals and activating the trigeminal nucleus in the brain stem [8] are considered to be triggers of migraine attacks, the exact mechanisms underlying the pathophysiology of the disease remain unclear and still are a matter of debate [9].

Recently, a case-control study showed that patients with PD were more likely to have CM [10]. It has been proposed that PD could act as a systemic inflammatory vascular stressor that contributes to the process of migraine chronification [11,12]. In addition, levels of sensory neuropeptides that were thought to be involved pathophysiology of migraine such as neurokinin A (NKA) and substance P (SP) [13] are increased in both the gingival crevicular fluid (GCF) [14,15] and plasma of PD patients [15]. Nevertheless, no information exists on the relationship between PD and migraine in a large multicentre sample of migraineurs.

The aim of this study was twofold: firstly to assess the prevalence of self-reported PD in migraineurs and, secondly to investigate whether there is an association between both diseases.

MATERIALS AND METHODS

We carried out a cross-sectional survey including consecutive migraineurs attending 12 Spanish Headache Units, between February and April, 2018. The study was conducted according to the Declaration of Helsinki of the World Medical Association (2008) and was approved by the Ethics Committee of the Servizo Galego de Saúde (date of approval: 10/05/2016 and ID: 2016/079). Each participant gave written consent after full explanation of the research purpose.

Neurological examination

Migraine diagnosis was based on the ICHD-3 beta International Headache Classification [16]. CM was defined as headache occurring on 15 or more days per month for more than 3 months. Patients were diagnosed with EM if they patient had less than 15 days/month of headache. In addition, we registered time of evolution of both migraine (in years) and CM (in months), number of days with headaches per month during the last 3 months, presence of aura and allodynia as well as family history of migraine. Preventives and symptomatic drugs for migraine were also recorded together with analgesic overuse.

Self-reported evaluation of PD

Diagnosis of PD was assessed by means of a validated self-reported questionnaire [17]. Among the 8 questions included in the questionnaire, the most conservative model to predict the presence of PD was the one that included the following questions: a) Do you think you might have gum disease?; b) Have you ever had any teeth become loose on their own, without an injury?; c) Have you ever been told by a dental professional that you lost bone around your teeth?; d) During the past three months, have you noticed a tooth that doesn´t look right? Therefore, a patient was considered to have PD if 1 of the 4 selected questions had a positive answer (i.e., yes).

Socio-demographic, medical and clinical data

By means of a structured questionnaire we obtained data regarding age, gender, education level, previous history of diabetes, hypertension, hypercholesterolemia, asthma, allergy, fibromyalgia, stress, anxiety, depression, alcohol consumption (≥14 g/day), tobacco smoking (≥10 cig/day), caffeine use (≥2-3 cups/day), physical activity (2-3 days/week). Body mass index (BMI) was calculated with the standard formula weight/height^2.

Statistics

IBM SPSS Statistics 20.0 Software for Mac (SPSS Inc., Chicago, IL, USA) was used to run all analyses. Normally distributed continuous data confirmed by Kolmogorov-Smirnov test are reported as mean ± standard deviation. Categorical variables are shown as percentages and compared by chi-square test. Unpaired Student´s t-test was applied to compare the mean values between groups. We constructed a series of logistic regression models with incremental adjustments for significant variables to ascertain the relationship between self-reported PD and CM. The significance level α for all tests was set at 0.05.

RESULTS

Six hundred and fifty-one migraineurs were included in the analysis. Characteristics of the whole population are shown in **Table 1**. Half of the patients presented a self-reported diagnosis of PD (N=327; 50.2%). Migraineurs with PD were significantly older (46.0±12.0 vs. 42.5±12.5, P<0.001), had more frequently a previous history of fibromyalgia (23.5% vs. 7.7%, P<0.001), stress (58.7% vs. 41.4%, P<0.001), anxiety (48.9% vs. 29.3%, P<0.001), depression (32.4% vs. 17.9%, P<0.001), and allodynia (52.0% vs. 30.2%, P<0.001). Moreover, this group of patients consumed more drugs such as topiramate (22.9% vs. 14.8%, P=0.008) and simple analgesics (32.1% vs. 13.9%, P<0.001) than migraineurs without PD as well as they performed less physical activity (26.3% vs. 38.9%, P=0.001) and had a lower educational level (26.0% vs. 19.4%, P<0.001). No significant differences were observed with regards to the remaining variables (data not shown).

Self-reported PD was present in 212 of 393 CM patients and in 115 of 258 EM patients. Accordingly, PD was significantly more prevalent in the CM group compared with EM subjects (53.9% vs. 44.6%, P=0.019; **Fig. 1**).

Of the whole sample, 60.4% were diagnosed with CM and 39.6% with EM. Chronic migraineurs had a significantly higher body mass index, prevalence of certain comorbidities (i.e., diabetes, fibromyalgia, allergy, depression, and anxiety) and allodynia as well as consumed more preventives and symptomatic treatment than patients with EM. As expected, CM patients presented more days of migraine attacks per month and analgesic overuse compared to the EM group. Furthermore, patients with CM performed significantly less physical activity and had a lower prevalence of high educational level (**Table 1**).

In the unadjusted logistic regression model, self-reported PD was significantly associated with the presence of CM (Table 2, Model I). Adjusting factors such as age, gender and BMI did not change the association (Table 2, Model II and III). The additional adjustment for education level, physical activity, fibromyalgia as well as psychiatric disorders such as

anxiety and depression showed attenuation in the likelihood of having CM if the participant was self-diagnosed with PD (Table 2, Model IV and V).

DISCUSSION

Overall, PD prevalence in migraineurs was higher than expected from employed Spaniards (50.2% vs. 38.4%) [1]. However, a study carried out in Austria showed that periodontal patients had a lower prevalence of self-reported migraine compared to those without PD [18]. In the present study, self-reported PD was more common in CM patients than in EM individuals. This finding is in accordance with previous results, in which approximately half of CM patients showed some degree of PD [10-12]. Furthermore, similar to a previous case-control study [10], self-reported PD was associated with CM with an OR of 1.456 (1.620-1.997). However, it has to be highlighted that after adjusting for all different covariates, a drop in the OR was noticed leading to a lack of statistical significance (OR=1.100; 95%CI:0.784-1.543, P>0.05).

It has been hypothesized that inflammation within the periodontal tissues is associated with the release of several pro-inflammatory molecules that could be involved in the onset of migraine attacks therefore facilitating migraine chronification. Our group found that PD was associated with increased peripheral concentrations of leptin and procalcitonin in patients with CM [11,12]. On the other hand, PD could also be responsible for the overexpression of neurogenic inflammatory mediators during free-headache periods in chronic migraineurs [19]. In this sense, it has been found that periodontal patients exhibited both local and systemically increased production of SP and NKA [14,15]. On contrary, CGRP was not detectable in GCF of PD patients [20]. It could be speculated that vasodilation produced by periodontal inflammation might elevate the net rate of CGRP removal from the gums and increase circulating CGRP levels, thus, promoting migraine chronification.

In the present sample of migraineurs, the progression of PD may have a different pattern due to the great variable of age between participants (minimum age: 18 and maximum age: 78). PD is more prevalent in older age groups as compared to younger groups. Nevertheless, PD might be more severe in elderly due to cumulative periodontal tissue destruction over lifetime rather than an age-related issue affecting host susceptibility [21]. Also it is worth mentioning that most of the subjects were females. Although it could be a factor that influences periodontal severity because data showed that in Spain men had more periodontal pockets than females (43.2% vs. 31.6%) [1], the high number of females in our migraine population is representative due to it is a disease that mainly affects females. When we compared CM with EM, however, no significant differences were found in terms of age. In

fact, after adjusting for age and gender self-reported PD remains significantly associated with CM (OR=1.406; 95%CI:1.022-1.935, P=0.036).

Our study has several shortcomings. The main limitation of the present survey is the use of a self-reported measure of PD [13]. Although diagnosis of PD is usually based on clinical measurements (i.e., periodontal pocket depth and attachment loss) and radiographic alveolar bone loss, self-reported measures of PD could be useful in studies with large samples due to reduction in time and convenience for clinicians as well as lower public costs [22]. In order to avoid an overestimation of PD prevalence that could occur using this type of tools, we applied the most conservative model to predict PD presence. Even though the questionnaire used in our investigation was validated in a representative sample of noninstitutionalized Americans civilians [17], differences from Spaniards in terms of oral hygiene and prevalence of PD could explain the higher number of subjects with PD in our sample. One of the reasons of observing a lower prevalence of PD in EM compared to CM, might be due to more than half of the migraineurs included in our survey had CM (60.4%). This could be because in Spanish hospitals, specialized Headache Units tend to treat complex cases (i.e., refractory migraines or CM) rather than mild headaches or EM. It is worth mentioning that migraineurs with PD were older and showed comorbidities such as psychiatric disorders (i.e., depression, anxiety, and stress) together with a lower educational level that could confound any potential association between PD and migraine. Indeed, adjustment for important covariates demonstrated an exponential attenuation of the association between self-reported PD and CM. However, a recent case-control study demonstrated that patients with PD were at a 2.4-fold increased risk for having CM independent of age, female sex, depression, obesity, and low educational level [10].

Within the limitations of the present survey, we can conclude that self-reported PD is common in migraineurs. Furthermore, the prevalence of self-reported PD is higher in CM than in EM. However, more evidence from epidemiological studies with large representative samples and using clinical PD diagnosis is needed to investigate if there is a relationship between both diseases.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: The authors have no conflicts of interest to declare.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participant included in the study.

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Table 1. Characteristics of the population study.

VARIABLES	All sample (N=651)	EM (N=258)	CM (N=393)
Sociodemographic and clinical data			
Age (years)	44.3±12.3	43.2±12.9	45.0±11.9
Females, n (%)	553 (84.9)	219 (84.9)	334 (85.0)
BMI (kg/m^2)	25.2±4.5	24.7±4.3	25.6±4.6**
Educational level, n (%)			
-Low	148 (22.7)	57 (22.1)	91 (23.2)
-Medium	286 (43.9)	97 (37.6)	189 (48.1)
-High	217 (33.3)	104 (40.3)	113 (28.8)**
Co-morbidities, n (%)			
Diabetes	36 (5.5)	8 (3.1)	28 (7.1)*
Hypertension	68 (10.4)	25 (9.7)	43 (10.9)
Hypercholesterolemia	83 (12.7)	33 (12.8)	50 (12.7)
Asthma	55 (8.4)	20 (7.8)	35 (8.9)
Allergy	135 (20.7)	41 (15.9)	94 (23.9)*
Fibromyalgia	102 (15.7)	19 (7.4)	83 (21.1)**
Stress	326 (50.1)	122 (47.3)	204 (51.9)
Anxiety	255 (39.2)	79 (30.6)	176 (44.8)**
Depression	164 (25.2)	38 (14.7)	126 (32.1)**
Daily habits, n (%)			
Alcohol consumption	6 (0.9)	2 (0.8)	4 (0.1)
Cigarette smoking	107 (16.4)	35 (13.6)	72 (18.3)
Caffeine consumption	207 (31.8)	87 (33.7)	120 (30.5)
Physical activity	212 (32.6)	103 (39.9)	109 (27.7)**
Migraine characteristics			
Aura, n (%)	189 (29.0)	74 (28.7)	115 (29.3)
Allodynia, n (%)	268 (41.2)	71 (27.5)	197 (50.1)**
Current migraine frequency during the last 3 months (days/month)	10.8±7.7	5.9±3.2	14.0±8.1**
Time of migraine evolution (years)	22.1±13.5	22.2±13.6	22.0±13.5
Time of chronic migraine evolution (months)			70.3±88.8
Relatives with migraine, n (%)	123 (18.9)	188 (72.9)	309 (78.6)
Analgesic overuse, n (%)	141 (21.7)	14 (5.4)	127 (32.3)**
Migraine preventive treatment in the last 3 months, n (%)			
Topiramate	123 (18.9)	27 (10.5)	96 (24.4)**
β-blockers	93 (14.3)	38 (14.7)	55 (14.0)
Amitriptyline	158 (24.3)	45 (17.4)	113 (28.8)**
Flunarizine	44 (6.8)	19 (7.4)	25 (6.4)
Onabotulinumtoxin A	345 (53.0)	60 (23.3)	285 (72.5)**
Antihypertensives	42 (6.5)	14 (5.4)	28 (7.1)
Others	137 (21.0)	42 (16.3)	95 (24.2)*
Migraine acute treatment in the last 7 days, n (%)			
Triptans	309 (47.5)	101 (39.1)	208 (52.9)**
NSAIDs	361 (55.5)	146 (56.6)	215 (54.7)
Simple analgesics	150 (32.0)	45 (17.4)	105 (26.7)**
Combined analgesics	73 (11.2)	25 (9.7)	48 (12.2)

BMI: body mass index; EM: episodic migraine; CM: chronic migraine; NSAIDs: nonsteroidal anti-inflammatory drugs.

*P<0.05 compared to EM; **P<0.01 compared to EM.

Table 2. Associations between self-reported PD with presence of CM.

		Self-reported PD	
		OR (95%CI)	***P-value***
CM	**Model I**	1.456 (1.062-1.997)	0.020
	Model II	1.406 (1.022-1.935)	0.036
	Model III	1.396 (1.014-1.924)	0.041
	Model IV	1.259 (0.906-1.750)	0.170
	Model V	1.100 (0.784-1.543)	0.581

Model I: unadjusted association. Model II: adjusted for age and gender. Model III: adjusted for age, gender and BMI. Model IV: adjusted for age, gender, BMI, education level and physical activity. Model V: adjusted for age, gender, BMI, education level, physical activity, fibromyalgia, anxiety and depression.

FIGURE LEGEND

Fig. 1. Prevalence of PD among subtypes of migraine.