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Factors associated with parietal cell autoantibodies in the general population☆

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ABSTRACT

The presence in serum of parietal cell autoantibodies (PCA) is a characteristic of autoimmune gastritis. We determined the prevalence of PCA in the general population and investigate their association with type 2 diabetes, insulin resistance and lifestyle factors related with autoimmune gastritis. A cross-sectional study was performed, involving 429 individuals enrolled in a cohort study of the general population of the Canary Islands. All participants underwent physical examination, provided a blood sample and responded to a questionnaire regarding health and lifestyle factors. Serum concentrations of PCA, soluble CD40 ligand (sCD40L), C-peptide and glucose (to determine insulin resistance) were measured. The association of PCA with the other factors was determined with bivariate analysis, and logistic regression models were used to adjust the associations for age and sex. The prevalence of PCA was 7.8% (95% CI = 10.3–5.3). The factors associated with PCA were female sex ($p = 0.032$), insulin resistance ($p = 0.016$), menopause ($p = 0.029$) and sCD40L ($p = 0.019$). Alcohol consumption ($p = 0.006$) and smoking ($p = 0.005$) were associated with low prevalences of PCA. After adjustment for age and sex, the association with PCA was confirmed for smoking (OR = 0.1 [0.0–0.9]), alcohol consumption (OR = 0.3 [0.1–0.9]), insulin resistance (OR = 2.4 [1.1–4.9]), female sex (OR = 2.4 [1.1–5.3]), sCD40L (OR = 3.7 [1.2–11.4]) and menopause (OR = 5.3 [1.2–23.3]). In conclusion, smoking and alcohol consumption acted as protective factors against the appearance of PCA in the general population, whereas female sex, menopause, insulin resistance and elevated serum sCD40L were risk markers for PCA. In patients who smoke or drink alcohol, clinicians should be cautious when using PCA to rule out autoimmune gastritis.

1. Introduction

The presence in serum of parietal cell autoantibodies (PCA) and less frequently, intrinsic factor autoantibodies (IFA), is a characteristic of autoimmune gastritis (AIG). This organ-specific disease leads to atrophy of the fundus and body of the stomach, but spares the antrum. In patients with AIG parietal and zymogenic cells are lost from the gastric mucosa, and a chronic humoral and cellular inflammatory infiltrate appears. The detection of PCA identifies individuals with asymptomatic AIG [1], the most common form of the disease before mucosal atrophy leads to iron malabsorption, ferropenic anemia, impaired vitamin B12 absorption [2] and pernicious anemia [3]. Parietal cell autoantibodies recognize the gastric proton pump (H^+/K^+-ATPase) of parietal cells in the gastric mucosa as an autoantigen [4].

The bacteria *Helicobacter pylori* is also involved in the etiology of AIG [5,6]. The annual incidence of the disease may be as high as 11% among individuals with *H. pylori* infection, and is less than 1% in noninfected persons [7]. *H. pylori* infection is linked to lifestyle [8] and has been related with type 2 diabetes [9] and insulin resistance (IR) [10]. However, to our knowledge there have been no attempts thus far to analyze the relationship between PCA and type 2 diabetes, IR or lifestyle factors linked to *H. pylori* infection.

Autoimmune gastritis is a risk factor for stomach cancer [11,12], and patients often have detectable serum concentrations of PCA [13] and elevated serum concentrations of the soluble CD40 ligand (sCD40L) [14]. However, it is not known whether PCA titers are associated with sCD40L levels in the general population.

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Table 1
Biological factors associated with parietal cell autoantibodies.

		n	Prevalence PCA (%)	*p*	OR (95% CI)
Sex	Women	262	10.7	0.032	2.2 (1.0–4.8)
	Men	167	4.8		
Insulin resistance	Resistance	192	11.5	0.016	2.4 (1.2–5.0)
	No resistance	235	5.1		
Menopause	Post-menopausal women	166	13.9	0.029	2.9 (1.1–8.0)
	Menstruating women	96	5.2		
sCD40L	Third tercile	51	15.7	0.019[a]	3.8 (1.2–11.4)[b]
	Second tercile	117	7.7		1.7 (0.6–4.9)[b]
	First tercile	127	4.7		1[b]

[a] *p* for trend.
[b] OR with respect to the first tercile.

The aims of this study were to determine the prevalence of autoantibodies associated with AIG in the general population of the Canary Islands, and to determine the relationships between PCA and (i) health problems (type 2 diabetes and IR), (ii) lifestyle factors known to be related with *H. pylori* infection, and (iii) serum sCD40L concentration.

2. Materials and methods

2.1. Study population and sample

This cross-sectional study involved 429 individuals selected from the participants in the "CDC de Canarias" cohort study (CDC is the acronym for *C*ardiovascular, *D*iabetes and *C*ancer). The study design and preliminary results were published elsewhere [15]. Briefly, the cohort is a random sample of the adult (aged 18–75 years) general population of the Canary Islands. A total of 6729 participants were enrolled between January 2000 and December 2005, and the participation rate was 70%. During their first appointment with the researchers, each participant underwent a complete physical examination and a blood sample was obtained after an overnight fast. In the course of a structured interview, each participant responded to the ad hoc questionnaire available at http://www.cdcdecanarias.org. Participants were considered to have diabetes if they reported having the disease and receiving treatment, or if their blood glucose concentration was 125 mg/dL or higher. Because it is clearly related with diabetes, obesity was also recorded (body mass index [BMI] $\geq$ 30 kg/m^2). Self-reported consumption of alcohol was categorized as none/negligible for <1.5 g/day, moderate for $\geq$1.5 to $\leq$30 g/day, and high for >30 g/day.

2.2. Serum concentrations

Blood samples were divided into aliquots of serum and stored at −80 °C until use in assays to measure autoantibody titers and laboratory values. Serum concentration of sCD40L was measured by ELISA with the R&D® kit (Minneapolis, MN, USA; pg/mL, intra-assay coefficient of variation 5.0%, inter-assay coefficient of variation 6.2%). Insulin resistance was determined with the HOMA2 model, which estimates resistance based on a combination of basal blood glucose and C peptide concentrations, according to information available from the Oxford Centre for Diabetes, Endocrinology & Metabolism (http://www.dtu.ox.ac.uk/homa). Concentrations of C peptide were measured with the Biosource International® assay (Camarillo, CA, USA; ng/mL, intra-assay coefficient of variation 4.7%, inter-assay coefficient of variation 6.3%). Blood glucose was measured in mg/dL with a Hitachi® autoanalyzer within 24 h after the blood sample was obtained.

2.3. Antibodies

To detect PCA we used an indirect immunofluorescence method (cytoplasmic staining of gastric mucosa parietal cells) at a starting dilution of 1:40 on sections of mouse gastric mucosa as the substrate (Zenit, Menarini, Florence, Italy). To detect IFA we used an ELISA with the manufacturer's recommended cut-off value (Zenit, Menarini). Assays to la detect IFA were done only in 36 samples that were positive for PCA [16].

2.4. Statistical analysis

The results for continuous variables are reported as the mean ± standard deviation, and the results for categorical variables are given as relative frequencies. Student's *t* test was used to compare mean values, and the chi-squared test was used to compare proportions. When the results were analyzed in 2 × 2 contingency tables, the odds ratio (OR) and 95% confidence interval (95% CI) were also calculated.

Multivariate analysis with adjustment for age and sex was done with logistic regression models in which the dependent variable was positive versus negative PCA and the independent variables included were age, sex and the factor of interest (smoking, alcohol consumption, IR, sCD40L level and menopause). In all models the goodness of fit was checked with the Hosmer–Lemeshow test. All analyses were done with version 19.0 (in Spanish) the Statistical Package for Social Sciences.

3. Results

Of the 429 samples analyzed (262 women and 167 men), PCA was positive in 36. The overall prevalence for the sample was 8.4%, and after weighting for sex distribution the overall prevalence was 7.8% (95% CI = 10.3–5.3). The prevalence was significantly higher for women (10.7%) than for men (4.8%, $p = 0.032$). The IFA assay was positive in 2 of 36 samples (5.6%), for a prevalence of 0.5% in the general population.

Mean age between PCA-positive and PCA-negative individuals did not differ significantly (53.0 ± 11.6 years versus 53.3 ± 11.4 years, $p = 0.893$). Table 1 shows the biological factors associated with an increased risk of a positive serum PCA finding: female sex ($p = 0.032$), IR ($p = 0.016$), menopause ($p = 0.029$) and sCD40L ($p = 0.019$).

Table 2 summarizes the findings for the relationship between PCA positivity and smoking, drinking and health-related lifestyle problems. Obesity and diabetes were not significantly related with PCA positivity. However, smoking and alcohol consumption showed significant associations: the prevalence of PCA in serum was lower among smokers (1.4%) than ex-smokers (4.0%) or non-smokers (11.9%; $p = 0.005$ for trend). The prevalence of PCA was also

Table 2
Relationship of parietal cell autoantibodies with lifestyle factors and related health problems.

		n	PCA prevalence (%)	*p*	Odds ratio (95% CI)
Smoking	Smokers	70	1.4	0.005[a]	0.1 (0.0–0.8)[b]
	Ex-smokers	99	4.0		0.3 (0.1–0.9)[b]
	Never smokers	260	11.9		1[b]
Drinking	>30 g/day	35	2.9	0.006[a]	0.2 (0.0–1.7)[b]
	1.5–30 g/day	122	3.3		0.3 (0.1–0.8)[b]
	<1.5 g/day	271	11.4		1[b]
Obesity	BMI ≥ 30	178	9.0	0.745	1.1 (0.6–2.2)
	BMI < 30	247	8.1		
Type 2 diabetes	Diabetes	140	9.3	0.642	1.2 (0.6–2.4)
	No diabetes	289	8.0		

[a] *p* for trend.
[b] OR with respect to no or negligible smoking or drinking.

lower in persons who consumed more than 30 g alcohol/day (2.9%) compared to moderate drinkers (3.3%) and nondrinkers or those who consumed negligible amounts of alcohol (11.4%; $p = 0.006$ for trend).

The associations of PCA with these factors were corroborated in the multivariate models adjusted for age and sex (Table 3). Smoking (OR = 0.1) and alcohol consumption (OR = 0.3) were the factors with the strongest protective effects against PCA positivity, whereas menopause (OR = 5.3) was the factor with the greatest risk for PCA positivity. Multivariate analysis also confirmed female sex, IR and sCD40L concentration as risk markers for PCA positivity (Table 3).

4. Discussion

We found that smoking and alcohol consumption had a strong protective association with PCA. In contrast, the greatest risk for PCA was seen in postmenopausal women. Other risk factors for PCA identified in our analysis were high sCD40L concentration, female sex and IR.

Smoking has been known for more than 50 years to be a risk factor for some gastrointestinal diseases [17]. In smokers, parietal cells produce larger amounts of acid, making the gastric mucosa more vulnerable the appearance of peptic ulcer [18]. In addition, smoking affects the immune system by modifying both humoral and cellular responses, and thus acts as a pro-inflammatory and inmunosuppressive agent [19]. Smokers have lower serum concentrations of IgG immunoglobulin than nonsmokers [20] and are more susceptible to bacterial infection, as shown by the finding that *H. pylori* infection is more frequent in people who smoke [21]. Accordingly, a higher prevalence of PCA in smokers would not be unexpected.

Paradoxically, our results show the opposite association, and we speculate that smoking may have a protective effect against AIG that might override the inflammatory effect of *H. pylori* infection. Cigarette smoke extract was shown to increase the amount and activity of H^+/K^+-ATPase in the mouse gastric mucosa [22], and there is evidence that the development of H^+/K^+-ATPase tolerance may be attributable to peripheral mechanisms [7]. In mice, the presence of the endogenous antigen promotes T cell tolerance to H^+/K^+-ATPase [23]; when smoking increases this enzyme, it may thus facilitate increased tolerance to the autoantigen. Dendritic CD11c+ cells, which are physically associated with H^+/K^+-ATPase-rich parietal cells, entrap this enzyme in vesicular compartments [24] and move through the perigastric lymph nodes, where they encounter cells presenting large amounts of antigen and T cells with specific receptors for H^+/K^+-ATPase epitopes that escape the mechanisms of central tolerance. This encounter stimulates the proliferation of antigen-specific naive T cells, and once highly pathogenic cells are destroyed, cells that are more susceptible to suppression by T regulatory cell remain [25]. In the presence of a high antigen load as a result of smoking, autoreactive T cell apoptosis and T regulatory cell activity may increase, and these phenomena may explain the lower frequency of PCA in smokers.

We found no earlier studies that associated alcohol consumption with lower serum concentrations of PCA. However, some research has documented a lower frequency of anti-*H. pylori* antibodies in moderate drinkers [26]. It has also been suggested that alcohol consumption may facilitate the elimination of *H. pylori* infection [27]. Our findings corroborate this possibility and suggest that the incidence of AIG may be lower in moderate drinkers.

The higher prevalence of PCA in women according to our analysis is consistent with the higher prevalence of AIG in the female sex [28]. We found a clear increase in the risk of developing PCA after menopause independently of age. It could be speculated that during a women's reproductive years, the estrogen-related Th2 response may counterbalance the Th1 response that occurs in AIG. After menopause this equilibrium is lost, allowing Th1 cytokines and their stimulatory effect on antibody production to predominate [29].

The relationships we found between PCA and IR may reflect the greater prevalence of PCA in persons with *H. pylori* infection [30]. As noted above, *H. pylori* infection was recently found to be related with IR [10]. In contrast, we found no association between PCA and obesity or diabetes, two other processes know to be related with IR although to date, no clear etiopathogenic relationship has been determined. The association between PCA and sCD40L is plausible, and may reflect a relationship between these two markers not only in patients with gastric cancer [31,32] but also in persons in the general population who may have asymptomatic gastritis. The evidence to date does not make it possible to rule out a role for *H. pylori* infection in this relationship.

A potential limitation of our study is its cross-sectional design, which does not allow us to draw causal relationships for the associations we found. However, reverse causality appears unlikely, i.e.

Table 3
Each row shows the odds ratio (OR) and 95% confidence interval for a logistic regression model with parietal cell autoantibodies as the dependent variable, after adjusting the effect of the independent variables for age and sex.

Independent variables	OR (95% CI)	*p*
Smoker[a]	0.1 (0.0–0.9)	0.042
Alcohol 1.5–30 g/day[a]	0.3 (0.1–0.9)	0.037
Ex-smoker[a]	0.4 (0.1–1.2)	0.100
Insulin resistance	2.4 (1.1–4.9)	0.022
Female sex[b]	2.4 (1.1–5.3)	0.037
sCD40L T3/T1	3.7 (1.2–11.4)	0.021
Menopause[b]	5.3 (1.2–23.3)	0.026

[a] With respect to nonsmokers or nondrinkers.
[b] Adjusted only for age.

an effect of PCA on (for example) smoking or alcohol consumption. Another limitation is that we did not investigate prior infection with *H. pylori*, although its relationship with PCA [30], alcohol [26,27] and tobacco [21] has been documented before, and in no way alters our conclusions.

On the other hand, a strength of this study is that it involved a sample of participants selected from the general population rather than a cohort of patients. Although other studies have been published about the prevalence of PCA, they included fewer individuals, groups of patients with different autoimmune diseases and healthy individuals [33–35].

In conclusion, the prevalence of PCA in this population is approximately 8%, although the prevalence is higher in women, particularly postmenopausal women. The prevalence is also higher in persons with elevated serum concentrations of sCD40L and with IR compared to the general population. Both smoking and drinking acted as protective factors against the appearance of PCA. In patients who smoke or drink alcohol, clinicians should be cautious when using PCA to rule out autoimmune gastritis.

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Conflict of interest

None.

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