Occupational, smoking and biomass fuel exposure in a cohort of Mexican patients with IgG4-related disease

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Abstract

Objective

To assess work history, occupational exposure, smoking, and biomass fuel use in a Mexican IgG4-related disease (IgG4-RD) cohort.

Methods

We conducted a cross-sectional study among patients with IgG4-RD. A standardised questionnaire was used to collect data on occupational, smoking, and biomass fuel exposure. The International Standard Classification of Occupations (ISCO88) categorised patients into white-collar (ISCO88 groups 0-5) and blue-collar (ISCO88 groups 6-9) work.

Results

We included 95 patients, with a mean age of 53.8±15.8 years, and 50.5% were male. Seventy-eight (82.1%) had paid work: 63 (66.3%) in white-collar and 15 (15.8%) in blue-collar occupations. Of those who had no paid work, 13 (13.7%) did household work and 4 (4.2%) were students. White-collar jobs were more common than blue-collar jobs, both including (66.3% vs. 29.5%) and excluding (66.3% vs. 15.8%) unpaid household work. Pancreatobiliary involvement was not more frequent among blue-collar workers. Occupational exposure was reported by 31.6% of patients. White-collar workers had more lung involvement (29% vs. 7.1%, p=0.02) and less biomass exposure (19% vs. 64.3%, p<0.001). Occupational exposures were associated with the proliferative phenotype (OR 3.5, 95% CI 1.08–11.36). History of smoking was linked to increased lung involvement (OR 3.2, 95% CI 1.1–9.4), while biomass exposure was associated with the Mikulicz/systemic phenotype (OR 2.6, 95% CI 1.03–6.9).

Conclusion

This study shows that there are different patterns of occupational exposure among Mexican IgG4-RD patients, with fewer blue-collar jobs compared to other cohorts. Smoking and biomass fuel exposure may be more significant risk factors for IgG4-RD in this population, warranting further investigation.

Key words

IgG4-related disease, occupational exposure, smoking, biomass, risk factors

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Introduction

IgG4-related disease (IgG4-RD) is a systemic immune-mediated fibroinflammatory condition characterised by mass-forming lesions composed of lymphocytes, IgG4+ plasma cells and varying degrees of fibrosis that can affect almost any organ, with a predilection for the major salivary and lacrimal glands, pancreas, biliary tract, and retroperitoneum, and if left untreated, it may lead to organ dysfunction (1-3).

As with most autoimmune and inflammatory diseases, the exact cause and triggers for the development of IgG4-RD are not known. Genetically, loci and polymorphisms that confer susceptibility to IgG4-RD have been described in different populations (4). Moreover, punctual mutations have been recently described as a cause of familiar IgG4-RD (5-7). Host factors such as current smoking, was reported as the first recognised modifiable risk factor for IgG4-RD, especially in patients with retroperitoneal fibrosis (8). Environmental asbestos exposure has also been suggested as a possible trigger of IgG4-RD (9). However, the evidence is limited to case reports.

The occupational environment, particularly in blue-collar occupations, a term that refers to manual labour occupations such as farming, construction work, and painting, is often associated with exposure to industrial chemicals, mineral dust, and other potentially harmful antigens.

This exposure has been linked to an increased risk of developing IgG4-RD of the biliary tract and pancreas. In a pilot study from the Netherlands and the United Kingdom, 88% and 61% of patients from Amsterdam and Oxford, respectively, reported having had a blue-collar job (10). Moreover, in a recent Dutch study, including 101 patients with IgG4-RD, the history of blue-collar work was associated with higher odds of developing IgG4-RD of the pancreatobiliary phenotype (11). The authors hypothesised that these findings could explain the striking male predominance of pancreatobiliary IgG4-RD.

IgG4-RD may exhibit different demographic and clinical behaviour depending on ethnicity (1, 3, 12). For instance, Latin-American IgG4-RD patients are younger at disease onset and male and female patients are equally represented compared to White and Asian cohorts (13, 14). As such, the same environmental or occupational risk factors may be different in this population.

Therefore, in the present study, we aimed to determine the prevalence of white-collar and blue-collar work, occupational exposure, smoking history, and biomass fuel use in a Mexican IgG4-RD cohort.

Patients and methods

We performed a descriptive cross-sectional study. We included patients diagnosed with IgG4-RD according to the 2020 revised Comprehensive Diagnostic Criteria and/or the 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria classification criteria for IgG4-RD attending a tertiary referral centre in Mexico City between 2018-2022 (15, 16).

Patients were categorised into clinical phenotypes according to the classification by Wallace *et al.*, which include pancreatobiliary, retroperitoneal/aortic, head and neck-limited, and Mikulicz/systemic phenotypes (12). Those that did not fit any of the previous phenotypes were assigned to the undefined group (13, 14). Patient were also divided according to the dichotomous phenotype classification described by Zhang and Stone as proliferative and fibrotic phenotypes (1).

A standardised questionnaire was applied to collect information regarding work, smoking and biomass fuel exposure history. Subjects who smoked at inclusion were defined as current smokers, those who had stopped smoking prior to inclusion as former smokers, and those who had never smoked before or at inclusion as never smokers. Total cigarette exposure, in pack-years, was calculated by multiplying the number of years the patient smoked by the packs smoked per day. Biomass fuel exposure was defined as exposure to burned organic matter and its particles, including wood, crop residue, animal dung, and charcoal, used for cooking, heating, and lighting (17).

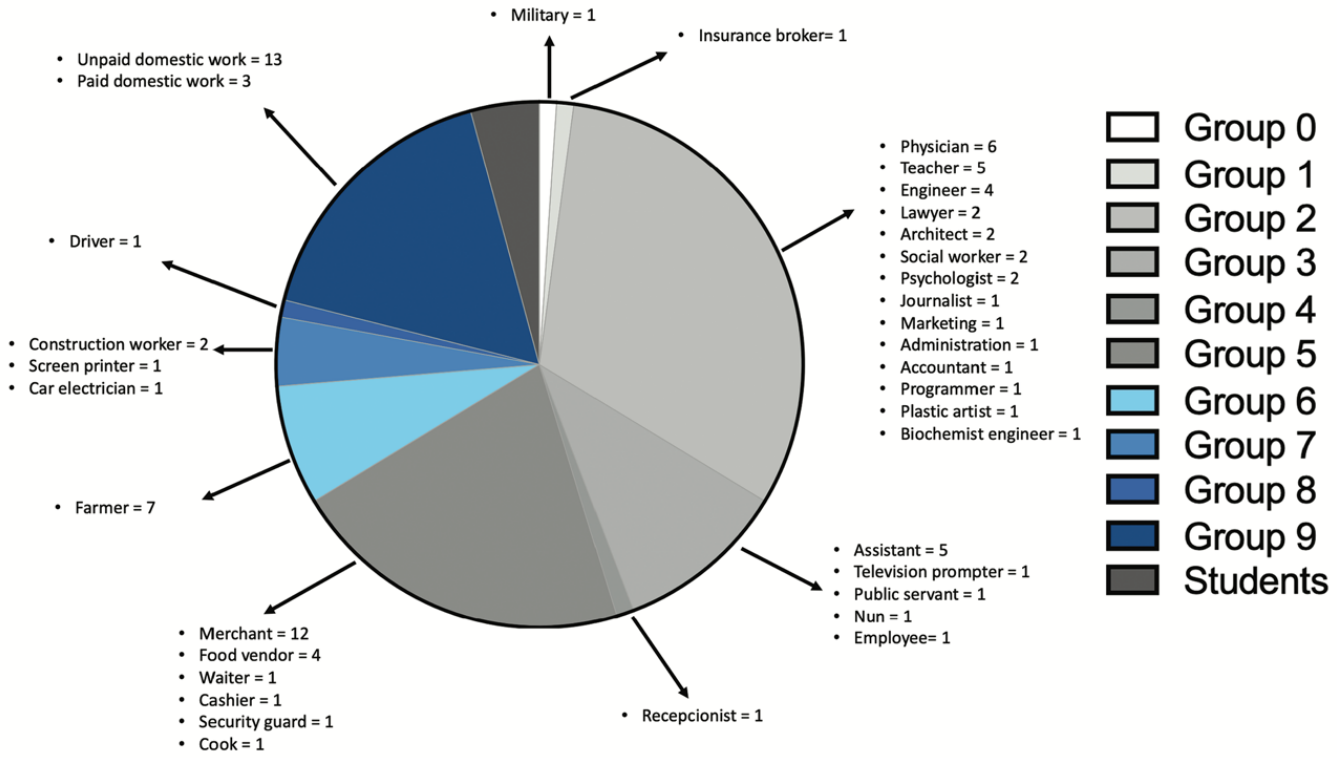

Fig. 1. Distribution of occupations according to ISCO88 groups.

We used the International Standard Classification of Occupations (ISCO88) to categorise the patients into those with white-collar (ISCO88 groups 0-5) or blue-collar (ISCO88 groups 6-9) work (11, 18). Unpaid household work was defined as work performed in or for a household, primarily by women, for their families (19, 20). Unpaid household work was classified within group 9. Students were excluded from the final analysis.

We obtained approval from the Institutional Review Board, and the study complied with the Declaration of Helsinki.

Statistical analysis

We used descriptive statistics. Dichotomous variables were expressed as absolute frequencies and continuous variables as means and standard deviations (SD) or medians and interquartile range (IQR). Categorical variables were analysed using Chi square or Fisher's exact test as appropriate. Comparison between means was made with the Student's t-test and between medians with the Mann-Whitney U-test. We used logistic regression analysis reporting OR and 95% CI. SPSS 20.0 and GraphPad Prism 10.1.1 were used for all the analyses.

Results

The study cohort comprised 95 patients, with a mean age of 53.8±15.8 years. Among them, 48 (50.5%) were male. The distribution of phenotypes was as follows: pancreatobiliary in 21 (22.1%), retroperitoneal/aortic in 8 (8.4%), head and neck–limited in 29 (30.5%), Mikulicz/systemic in 25 (26.3), undefined in 12 (12.6%), proliferative in 67 (70.5%), and fibrotic in 28 (29.5%).

A total of 78 patients (82.1%) had paid occupations, with 63 (66.3%) engaged in white-collar work and 15 (15.8%) in blue-collar work. Of those without paid occupations, 13 (13.7%) performed household work and 4 (4.2%) were students. Figure 1 illustrates the distribution of occupations according to ISCO88 groups.

The proportion of patients with white-collar work was significantly higher compared to those with blue-collar work, both when unpaid household work was included within the blue-collar group (63 [66.3%] *vs*. 28 [29.5%]) and when it was excluded (63 [66.3%] *vs*. 15 [15.8%]).

We found no significant differences in the proportion of patients with pancreatobiliary phenotype (14 [22.2%] *vs*. 5 [33.3%], p=0.40), pancreatic involvement (29 [46%] *vs*. 10 [35.7%], p=0.35), or biliary involvement (20 [31.7%] *vs*. 6 [21.4%], p=0.31) between white-collar and blue-collar workers (Table I). Patients with white-collar occupations had a higher prevalence of lung involvement (18 [29%] *vs*. 2 [7.1%], p=0.02) and lower exposure to biomass (12 [19%] *vs*. 18 [64.3%], p<0.001) compared to their blue-collar counterparts. These findings were consistent even when unpaid household work was excluded from the analysis (data not shown).

Occupational exposures were reported in 30 patients (31.6%). These exposures included (non-mutually exclusive): pesticides (n=8), aromatic solvents (n=8), mineral dusts (n=8), detergents (n=4), fertilisers (n=3), polycyclic aromatic hydrocarbons (n=3), plastic powders (n=2), gas fumes (n=2), and one case each of ionising radiation, metals, asbestos, toluene, biological dust, and paraffin.

When comparing the group with occupational exposure to those without it, there was a higher frequency of patients with the proliferative phenotype (25 [86.2%] *vs*. 43 [63.6%], p=0.02),

Table I. Demographic, exposure, clinical and serological characteristics of IgG4-related disease patients.

	White-collar work (n=63)	Blue-collar work (n=28)	*p*
Male, n (%)	35 (55.6)	12 (42.9)	0.26
Age, years, mean ± SD	55.7 ± 14.6	53.9 ± 15.1	0.54
Occupational exposure, n (%)	13 (20.6)	16 (51.1)	0.001
Smoking history, n (%)	31 (49.2)	13 (46.4)	0.80
Biomass fuel exposure, n (%)	12 (19)	18 (64.3)	<0.001
Phenotype			
Pancreatobiliary, n (%)	14 (22.2)	6 (21.4)	0.93
Retroperitoneal/aortic, n (%)	7 (11.1)	1 (3.6)	0.24
Head and neck-limited, n (%)	18 (28.6)	9 (32.1)	0.73
Mikulicz/systemic, n (%)	17 (27)	8 (28.6)	0.87
Undetermined, n (%)	7 (11.1)	4 (14.3)	0.66
Proliferative, n (%)	44 (69.8)	19 (67.9)	0.85
Fibrotic, n (%)	19 (30.2)	9 (31.1)	0.85
Organ involvement			
Orbit, n (%)	18 (29)	9 (32.1)	0.73
Lacrimal gland, n (%)	21 (33.3)	12 (42.9)	0.38
Submandibular, n (%)	27 (42.9)	13 (46.4)	0.75
Parotid gland, n (%)	16 (25.4)	9 (32.1)	0.50
Lymph nodes, n (%)	29 (46)	13 (46.4)	0.97
Lung, n (%)	18 (29)	2 (7.1)	0.02
Aorta, n (%)	2 (3.2)	1 (3.6)	0.92
Pancreas, n (%)	29 (46)	10 (35.7)	0.35
Biliary tract, n (%)	20 (31.7)	6 (21.4)	0.31
Retroperitoneum, n (%)	6 (9.5)	1 (3.6)	0.32
Kidney, n (%)	18 (28.6)	6 (21.4)	0.71
Serology			
High IgG4 levels, n+/n (%)	40/62 (64.5)	17/27 (63)	0.88
IgG4, median (IQR), mg/dL	300 (96.2-799)	249 (90-372)	0.57
Hypocomplementemia, n+/n (%)	20/49 (40.8)	6/23 (26.1)	0.22
C3, median (IQR), mg/dL	116 (88-148.5)	124 (94-147)	0.94
C4, median (IQR), mg/dL	21.5 (10-33)	23.5 (17.5-35.7)	0.45
Eosinophilia, n+/n (%)	14/61 (23)	4 (14.3)	0.34
Eosinophil count, median (IQR), /mm^3	170 (73-364.5)	200 (100.5-324.8)	0.82

IQR: interquartile range; SD: standard deviation.

submandibular gland involvement (17 [58.6%] *vs*. 23 [34.8%], *p*=0.03), and eosinophilia (9 [32.1%] *vs*. 9 [13.8%], *p*=0.04). There was also a tendency towards the Mikulicz/systemic phenotype (11 [37.9%] *vs*. 14 [21.2%], *p*=0.08). At the logistic regression analysis, the variable that remained associated with occupational exposure was the proliferative phenotype (OR 3.5, 95% CI 1.08-11.36, *p*=0.03).

Forty-one patients (43.2%) patients reported active smoking, with a median of 3 (IQR 0.6–19.3) pack-years; 34 (35.8%) were former smokers, and 7 (8.4%) were current smokers. Passive smoking was reported by 4 (4.2%) patients, and 30 (31.6%) were exposed to biomass fuel.

When analysing patients with a smoking history compared to the group without exposure, there was a higher frequency of lung involvement (14 [31.1%] *vs*. 6 [12.2%], *p*=0.02; OR 3.2, 95% CI 1.1–9.4) in the former group. When comparing patients exposed to biomass fuel with those without exposure, there was a higher frequency of Mikulicz/systemic phenotype (12 [40%] *vs*. 13 [20%], *p*=0.04; OR 2.6, 95% CI 1.03-6.9) in the former group.

Discussion

Our study reveals notable differences in occupational exposure in Mexican patients with IgG4-RD, shedding light on potential regional differences in risk factors. Contrary to findings of studies from the Netherlands and the United Kingdom, where a high prevalence of blue-collar work was observed among IgG4-RD patients, our cohort exhibited a significantly lower prevalence of blue-collar work. Only 15.8% of our patients had blue-collar occupations compared to the much higher percentages reported by De Buy Wenniger *et al*. and Hubers *et al*. (10, 11). Additionally, pancreatobiliary involvement was not found to be more frequent in patients with blue-collar jobs. These disparities suggest that occupational exposure may not be the primary risk factor for IgG4-RD in the Mexican population.

Hubers *et al*. reported that more than 70% of their IgG4-RD cohort had relevant occupational exposure to industrial compounds, suggesting that this exposure might be the cause of the increased risk of IgG4-RD in blue-collar workers. Their study identified specific compounds that influence the likelihood of developing IgG4-RD, namely mineral dusts, asbestos, vapours, gases, and fumes (11). In contrast, we found that the frequency of occupational exposure was less than half of what they reported, although there were cases exposed to the same specific compounds associated with the risk of developing IgG4-RD.

Interestingly, we found that white-collar group had a higher prevalence of lung involvement, and the occupational exposure group was more likely to belong to the proliferative phenotype and had more submandibular gland involvement and eosinophilia, suggesting that occupational exposures may influence the clinical manifestations of IgG4-RD.

Recently, current smoking was identified as the first recognised modifiable risk factor for IgG4-RD, especially in women and those with retroperitoneal fibrosis (8). The prevalence of smoking in our cohort was similar to that study; however, we found no difference in the frequency of sex or retroperitoneal involvement between those with a smoking history and those without. Nonetheless, we observed a higher frequency of lung involvement in those with a history of smoking, suggesting that exposure to cigarette smoke components may be a risk factor for lung involvement in IgG4-RD, similar to what has been described in rheumatoid arthritis (21).

Interestingly, we found a considerably high prevalence of biomass exposure in our cohort. This prevalence exceeds the overall percentage of the Mexican population exposed to biomass fuels

for cooking, which is estimated to be around 18% (22). Household air pollution from solid fuel is a known risk factor for many respiratory conditions such as chronic obstructive pulmonary disease and lung cancer and has been associated with an increased risk of arthritis in a study conducted in low and middle-income countries (17, 23). Therefore, we hypothesise that household air pollution from biomass fuel may be a risk factor for IgG4-RD. Since women are more exposed to biomass fuel than men, this could explain the almost equal male-to-female ratio of IgG4-RD in Latin America (13, 14, 17). Moreover, exposure to this type of air pollution may influence the clinical expression of IgG4-RD, as evidenced by a higher frequency of the Mikulicz/systemic phenotype in this group.

We acknowledge several limitations in our study. First, it was a descriptive study rather than a population-based epidemiologic study. As such, only associations can be inferred. Second, we did not have a control group to compare the prevalence of white-collar and blue-collar work. Third, we did not quantify the extent of occupational or biomass fuel exposure. Finally, our cohort may not be representative of the entire Mexican population, because our centre is a referral centre in an urban setting. However, our centre treats individuals of all educational and social levels, making a bias toward a predominantly white-collar professional population unlikely.

In summary, our study found a significantly lower prevalence of blue-collar occupations in a Mexican IgG4-RD cohort compared to Dutch studies. This suggests that occupational exposure may not be a primary risk factor for IgG4-RD in Mexico. Instead, smoking and exposure to biomass fuels may play a greater role. Given the considerably high prevalence of biomass exposure in our cohort, further large-scale epidemiologic studies in countries with high biomass fuel use are needed to replicate our findings and to explore the timing of exposure, the dose-response relationship, and the possible mechanisms of disease development.

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