IOSR Journal of Nursing and Health Science (IOSR-JNHS)
e-ISSN: 2320–1959.p- ISSN: 2320–1940 Volume 12, Issue 1 Ser. I (Jan. – Feb. 2023), PP 33-37
www.iosrjournals.org

Occupational and environmental exposures in Interstitial Lung Abnormalities.

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Abstract
Background: *Interstitial Lung Abnormalities [ILA] have been reported in different cohorts between 7-9% of the studied population, as an incidental finding in asymptomatic subjects, in whom the interstitial disease is not suspected. History of smoking and advanced age is well known among other risk factors. Occupational and domestic exposures have a high prevalence in patients with interstitial lung diseases (ILD), therefore this study aimed to determine if the occupational and domestic exposures are related to the presence of ILA.*
Methods: *We evaluated 154 individuals from our "Lung Aging Program" in México City, 81 patients ILA and 73 control,we applied by telephone (due to the COVID-19 pandemic) a specific questionnaire designed for the study of patients with ILD.*
Results: *ILA groupwere older [70±6 versus 68±6 years p=0.04], and mostly of female gender [58vs75% p=0.02]. We found an association with bird exposure [OR 2.9 (95%CI 1.4-5.75) p= 0.002], we corroborate association of smoking [OR 3.12 (95%CI 1.6-6.05) p=0.0007], and we found that the exposure to molds as a risk factor for the development of ILA [OR 17.72 (95%CI 2.28-137.39) p=0.0001].*
Conclusion: *Our results show an association in the exposure to birds and mold with the development of ILA.*

Date of Submission: 27-12-2022 Date of Acceptance: 07-01-2023

I. Background

Interstitial Lung Abnormalities [ILA] have been reported in different cohorts between 7-9% of the studied population [1-5]. They are identified as areas of increased density on High-Resolution Computed Tomography (HRCT) [6] and could be an incidental finding in asymptomatic patients in whom the interstitial disease is not suspected. ILA is characterized by any of the following lesions: Ground glass opacities, reticular abnormalities, diffuse central nodules, honeycomb, traction bronchiectasis, and non-emphysematous cysts involving at least 5% of any lung lobe. [7,1]

Recently, it was proposed that ILA could be classified according to their location and the presence of fibrosis in ILA without subpleural predominance, ILA with subpleural predominance but without the presence of fibrosis, and ILA with subpleural predominance and fibrosis [1].

The prevalence of ILA in patients with a history of smoking and advanced age is well known [8]. Other risk factors that have been associated with its development include exposures to vapors, gas, dust [9] the presence of a serum increase of matrix metalloprotease [MMP]-7, interleukin-6, and galectin 3. Likewise, the presence of a MUC5B polymorphism promoter (rs35705950) [2] increases the risk.

On other hand, environmental air pollution contributes to a variety of lung and systemic diseases, and it has been increasingly implicated in adverse health outcomes [10]. Similarly, occupational and domestic exposures have a high prevalence in patients with interstitial lung diseases (ILD), being a critical factor for future research in the development of these diseases [11].

For this reason, this study aimed to determine if the occupational and domestic exposures are related to the presence of ILA.

II. Methods

Study Design and patient selection

This is a cross-sectional study that included 154 individuals from our "Lung Aging Program" at the Instituto Nacional de Enfermedades Respiratorias, in México City from March 2015 until June 2019. We applied by telephone (due to the COVID-19 pandemic) a specific questionnaire designed for the study of patients with interstitial lung diseases between August– February 2021. The questionnaire included demographic data, smoking, occupational with exposures to fumes, vapors, dust or chemicals, use of illicit drugs, exposures at home such as birds, down pillows or duvets, exposure to moisture and mold, and exposure

to isocyanates such as aerosols, industrials glues, and insecticides. The questionnaire allowed the subject to answer the survey with a yes or no to the specific questions. (**Additional File 1**)
Exposures were classified into four categories: 1.- Birds: this category included living with ornamental birds, pigeons, poultry, and use of quilts or pillows with feathers, 2. - Occupation: included work in construction and demolition, carpentry, metal casting, and house cleaning. 3.- Hobby: in this category, we included different

kinds of painting such as oil painting as well as aerosols or sprays and gardening, 4.- Others: this category included mold which was interrogated as to the presence of damage to the walls due to humidity or ceiling, living in an old house in the last ten years, poorly ventilated places, habitual loss of water in places such as the kitchen and the presence of discolored wardrobe with thin white or black layers covering them as well as leather clothes or shoes, hydro-massage at home, smoking and family inheritance history of interstitial lung disease.
The exposure was considered positive if the patient reported to have it directly at some time in his life or if he/she was still with the exposure. Demographic data and comorbidities were obtained from the clinical records.

Ethical approval
This protocol was approved by the ethical committee of the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (Protocol number C39-14), and all patients signed informed consent to participate in research studies.

All the methods (questionary applied) were performed following the relevant regulation to maintain the privacy of the patients.

This study was supported by CONACYT, grant: FOSISS 290645 awarded to IB-R

Statistical Analysis
The quantitative variables are presented as means and standard deviation and the percentages and frequencies were calculated for the qualitative variables. For the comparison of the variables, nonparametric U Mann-Whitney and Fisher's exact test were used, we estimate Odds Ratios with 95% confidence interval. Microsoft Excel version 2016 program was used to the database and Epi Info and GraphPad prim 8 for the analysis of results.

III. Results

One hundred and fifty-four individuals were evaluated, eighty-one subjects had interstitial lung abnormalities and seventy-three without ILA were analyzed as the control group (ctrl). Demographic characteristics are shown in **Table 1**. Individuals in the ILA group were older, (70 ± 6 versus 68 ± 6 years; p=0.04), and mostly of female gender (58 vs 75%; p=0.02). No significant differences were found in other demographic variables (**Table 1**).

Table 1.
Demographic and clinical characteristics of ILA and Control group

Characteristics	ILA n =81	Ctrl n =73	p-value
Age, yr. (± SD)	70 ± 6	68 ± 6	0.04
Gender, female (%)	47 (58)	55 (75)	0.02
Diabetes mellitus (%)	23 (28)	18 (24)	0.71
Hypertension (%)	32 (39)	21 (29)	0.17
BMI kg/m2 (± SD)	26 ± 4	27 ± 3	0.13

Yr, years, BMI: body mass index, ILA: Interstitial Lung Abnormalities, Ctrl: control group, SD: standard deviation.

The different groups of variables studied are shown in **Table 2**. In the group of birds, we found an association as a risk factor [OR 2.9 (95%CI 1.4-5.75); p=0.002], while in the group of others we corroborate the association of smoking [OR 3.12 (95%CI 1.6-6.05); p=0.0007], and we also found that the exposure to molds as a risk factor for the development of ILAs (OR 17.72 (95%CI 2.28-137.39); p=0.0001).

Table 2
Exposures associated with the development of ILA

Variable	ILA n = 81	Ctrl n = 73	OR	p-value
Birds (%)	38 (47)	17 (23)	2.9 (1.4 - 5.8)	0.002
Smoking (%)	49 (60)	24 (32)	3.12 (1.6 - 6.05)	0.0007
Mold (%)	16 (20)	1 (1)	17.72 (2.28-137.39)	0.0001
ILA: Interstitial Lung Abnormalities, Ctrl: control group, OR: Odd Ratio				

IV. Discussion

Due to the importance that ILA have taken in recent times and its association with an increased risk of all-cause mortality, in different investigations multiple risk factors have been associated with its development, among them the exposure of elemental carbon which also showed an association with their progression[3], but occupational and environmental exposures that have shown a significant prevalence in ILD[11]was not evaluated to the development of ILA.

In this study, we found an association between the development of ILA and the exposition to smoking, birds, and mold, this last one has been associated with different respiratory pathologies such as allergic respiratory disease, asthma, allergic rhinitis, and Hypersensitive Pneumonitis (HP). HP is an ILD whose association with mold or bacterial exposure is well known. The avian antigen is the most frequently identified cause of HP, nevertheless, indoor mold should be considered with the same relevance [12]. It has been observed that occupational Hypersensitivity Pneumonitis associated with mold presents what we know as "farmer lung", which has a prevalence with emphysema of 10% [13].

De Sadeleer et al. found a high prevalence between birds 53% and mold 20% with HP. Patients with Fibrotic HP had more often mold exposure and less often bird exposure compared to No Fibrotic HP, in addition to this, bird-exposed HP patients had better survival compared to mold-exposed patients [14], which is why indoors mold should be considered with a higher relevance as a risk factor. Interestingly, ILA patients in our cohort are respiratory asymptomatic and patients with exposure to birds show pattern subpleural predominance and fibrosis in 84% while patients exposed to mold showed 75%, this suggests that the relation between exposure and pattern is different to HP.

Our group has reported previously that some miRNAs in serum have been shown in patients with ILA. These regulated different pathways that are associated with aging/cellular senescence, inflammatory response, cancer, and lung fibrosis, which include transforming growth factor-beta (TGF-ß), Wnt, mammalian target of rapamycin (mTOR), Insulin, mitogen-activated protein kinase (MAPK) signaling, and senescence [15]. Furthermore, in another study, we showed that the loss of KLRG1 expression was associated with a highly proliferative and excessive functional activity of CD4+T cells in patients with ILA [16]. These suggested an inflammatory state that with the appropriate risk factors can trigger the development of ILA.

Our study has several limitations. First, we apply the clinical history of interstitial diseases via telephone (due to COVID-19 pandemic) for which there is a memory bias of the patients, likewise, the intensity, frequency, and duration of the different exposures evaluated are unknown. Another important limitation during our research is that our patients ignored the fact of the appropriate use of protection during the time of exposure, which could influence the evolution of the patient. But the association between mold and ILA is very clear.

In summary, the results described in this article propose that if there is any predisposition that together with the exposure factors described could present two different paths: develop ILA or HP. So, the early identification and elimination of these risk factors could be considered as a preventive measure in the natural history of ILA. We consider that exposure to these factors should be intentionally sought when approaching patients with ILA.

Acknowledgments: Dr. Alexia Palma-Lopez and Dr. Hiram Aguilar-Duran to apply the questionary.

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Additional Files

Additional File 1: Questionnaire applied by telephone, allowed the subject to answer the survey with a yes or not to the specific questions.

Please answer yesor not if you have been exposed to the following:

Home

Ornamental / pet birds (parrots, ducks, pigeons, turkeys)
Colombofilia
Duvet / pillow / feather mattress
Poultry / Farms
Central air conditioning / ventilation system
Old house in the last 10 years
Moisture damage to walls or ceiling
Dishwasher or kitchen sink regularly leaks water
Whirlpool / Jacuzzi in the poorly ventilated bathroom
Cabinet walls are discolored or have a thin layer of white or black covering them (mold)
Stored leather clothing or shoes with a thin layer of white or black covering it (mold)
Birds arriving on balcony, roof, garage
Smoking
Illicit Drugs
family inheritance history of interstitial lung disease

Job Occupation

Hay / Straw / Grains
Malt worker, barley germination, brewer
Mushroom / mushroom / shitake hatchery
Woods / Sawdust / Carpenter, Cedar, Mahogany, Oak Exposure
Landscaping or compost worker usually
Animal breeder (horses, cows)
Cheeses (aged, with mushrooms)
Cork industry (cork oak bark)
Leatherworking
Talks
Painting (spray or aeorosols)
Foam
talcum powder
Aluminum
House cleaning
Paper production

Cement
Isocyanates
Painting
Industrial glues
Insecticides
Rubber
Cotton
Demolition
Foundry
Ceramics
Plumbing
Metallurgical
Textile
Carpentry
Wood (felling)

Maria Jose Aguirre-Gonzalez, et. al. "Occupational and environmental exposures in Interstitial Lung Abnormalities." *IOSR Journal of Nursing and Health Science (IOSR-JNHS)*, 12(1), 2023, pp. 33-37.