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Environmental Factors (External Exposome) and Rare Immunological Diseases (Systemic Lupus Erythematosus): Is Smoking a Risk Factor or Protective Factor?

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Abstract **Original Research Article**

Introduction*:** The interaction between genetic and environmental factors influencing susceptibility to the development of systemic lupus erythematosus (SLE) is widely described in the literature. The strongest epidemiological evidence, largely from the North, exists in favor of an increased risk of SLE associated with exposure to current smoking, and a protective effect of moderate alcohol consumption associated against the development of SLE. The north-south differences in genetic and environmental characteristics in patients with SLE is openned research question in literature. We do not know whether there is a contrast between these genetic and environmental characteristics of lupus patients from the Northern society and those from the Southern society, particularly Malian lupus patients. The aim of this study was to determine external exopsome such sociodemographic and environnemental factors associated with increasing or decreasing risk to develop the systemic lupus erythematosus. ***Method*:** We conducted a cross-sectional study with retropective data collection from the medical records of patients hospitalized for autoimmune and/or autoinflammatory diseases in the Department of Internal Medicine at the University Hospital Center of the Point G between January 01, 2005 to December 31, 2019, i.e. 15 years. We performed a univariate analysis to obtain mean and standard deviation for quantitative data and numbers and percentages for qualitative data. In the bivariate analysis, the Chi-square and Fisher´s exact tests were used to assess the statistical significance and strength of the associations between the categorical independent variables (age, age group, sex, lifestyle) and the outcome variables (systemic lupus erythematosus). Variables with a Chi-square test with $p < 0.2$ at bivariate analysis were included in a multivariate logistic regression. ***Results: Globally, 6383 patients were hospitalized among which 317 patients presented autoimmune and or autoinflammatoire diseases. Out of the 317 patients, 43 patients presented the systemic erythematosus lupus, which a hospital frequency of 0.63%. For the lupus patients, females accounted for 93.02% with a Male to female sex-ratio of 0.08. Patients under 45 years represented 72.56% of the study population. One patient smoked the tobacco, one patient consumed the alcohol and one patient abused the drug (2.33%, each). Female (aOR= 8.32; 95% CI= 2.50 – 27.67; p= 0.001) remained factors that significantly influenced the development of SLE; patients under 45 years (aOR= 0.33; 95% CI= 0.13 – 0.89; p= 0.028) were found to be factors that were significantly associated with a decreasing risk to develop the SLE; and the smoking was not found to be a protective factor independently associated with the occurrence of SLE (aOR= 2.42; 95% CI= 0.30 - 19.70; p= 0.408). ***Conclusion*:** Although systemic lupus erythematosus is more common in non-smokers than smokers in our study, suggesting a

protective role of smoking, smoking was not found to be an independently associated protective factor for the development of systemic lupus erythematosus. Age over 45 years is significantly associated with a reduced risk of developing systemic lupus erythematosus. Female gender is a factor independently influencing the development of systemic lupus erythematosus.
Keywords: Smoking, Environmental Factor, External Exposome, Systemic Lupus Erythematosus, Rare Immunological Diseases.

INTRODUCTION

The interaction between genetic and environmental factors influencing susceptibility to the development of systemic lupus erythematosus (SLE) is widely described in the literature [1, 2]. In addition, Rania *et al*., conclude that the SLE can be environmentally induced [2].

Indeed, the exposome is a concept used to describe environmental exposures that an individual encounters throughout life, and how these exposures impact biology and health [3]. It has become a useful tool in understanding the interplay between genetics and environmental factors in the development of diseases, with a particular focus on chronic conditions [4]. The exposome is subdivided into three main components : i) external exposome includes general external factors, such as air pollution, diet, and socioeconomic factors, as well as specific external factors like chemicals and radiation; ii) internal exposome comprises endogenous factors, such as hormones, inflammation, oxidative stress, and gut microbiota; and iii) biological response refers to the resulted factors from complex interactions between the external and internal that can influence on an individual's physiology and health [4, 5].

The systemic lupus erythematosus, one of rare immunological diseases, is a chronic inflammatory autoimmune and multi-systemic disease that is characterized by the production of autoantibodies and tissue deposition of immune complexes [6, 7].

Today, there are thousands of chemicals in the environment and it is well-established that individuals are exposed to different combinations of chemicals depending on their location, occupation, and lifestyles [5].

The strongest epidemiological evidence, largely from the North, exists in favor of an increased risk of SLE associated with exposure to current smoking, and a protective effect of moderate alcohol consumption associated against the development of SLE [1-8].

The north-south differences in genetic and environmental characteristics in patients with SLE is openned research question in literature. We do not know whether there is a contrast between these genetic and environmental characteristics of lupus patients from the Northern society and those from the Southern society, particularly Malian lupus patients.

The aim of this study was to determine external exopsome such sociodemographic and environnemental factors associated with increasing or decreasing risk to develop the systemic lupus erythematosus.

METHOD

We conducted a cross-sectional study with retropective data collection from the medical records of patients hospitalized for autoimmune and/or autoinflammatory diseases in the Department of Internal Medicine at the University Hospital Center of the Point G between January 01, 2005 to December 31, 2019, i.e. 15 years. Patients seen in the outpatient consultation for autoimmune and auto-inflammatory diseases in the internal medicine department at the University Hospital Center of the Point G and patients hospitalized outside the study period for autoimmune and auto-inflammatory diseases in the internal medicine department at the University Hospital Center of the Point G were not included in this study. This was an exhaustive sampling of all cases of hospitalization for autoimmune and/or auto-inflammatory diseases during the study period. A pre-established survey form was designed and used to collect on the sociodemographic, lifestyle and clinical data from medical records and also registry of hospitalization. The collected data were entered into SPSS version 22 software for cleaning and analysis. We conducted statistical analyses using Epi Info version 7.2 and SPSS version 27 software. We used Microsoft Excel to generate bar graphs. We performed a univariate analysis to obtain mean and standard deviation for quantitative data and numbers and percentages for qualitative data. In the bivariate analysis, the Chi-square and Fisher´s exact tests were used to assess the statistical significance and strength of the associations between the categorical independent variables (age, age group, sex, lifestyle) and the outcome variables (systemic lupus erythematosus). Variables with a Chi-square test with $p < 0.2$ at bivariate analysis were included in a multivariate logistic regression. The medical records and registry of hospitalization were used in strict confidentiality and were returned and filed in the archive room immediately after exploitation.

RESULTS

Univariate analysis of socio-demographic and lifestyle data: during the study period from January 01, 2005 to December 31, 2019, 6383 patients were hospitalized among which 317 patients presented autoimmune and or autoinflammatoire diseases. Out of the 317 patients, 43 patients presented the systemic erythematosus lupus, which a hospital frequency of 0.63%. For the lupus patients, females accounted for 93.02% with a Male to female sex-ratio of 0.08. Patients under 45 years represented 72.56% of the study population. One patient smoked the tobacco, one patient consumed the alcohol and one patient abused the drug (2.33%, each) (table 1). Males were slighly oldest than females according to our study population (figure 1). The systemic lupus erythematosus occurred earlier in women than in men (figure 2).

Bivariate analysis of factors associated with systemic lupus erythematosus: The non-smokers were 7.18 times more likely than smokers to develop SLE (OR= 7.18; 95% CI= 0.96 – 53.65; p= 0.055). SLE were 8.68 times more likely to be found in females than in males (OR= 8.68; 95% CI=2.62 – 28.74; p=0.000). Patient over 45 years (OR= 0.31; 95% CI= 0.12 – 0.81; p= 0.017) were less likely than the patient under 45 years to develop SLE (table 2).

Multivariate analysis of factors associated with SLE: the results from the logistic regression analyses that included variables significantly associated with SLE from the Chi-square test of independence. Adjusting for the factors simultaneously, female (aOR= 8.32; 95% CI= 2.50 – 27.67; p= 0.001) remained factors that significantly influenced the development of SLE; patients under 45 years (aOR= 0.33; 95% CI= 0.13 – 0.89; p= 0.028) were found to be factors that were significantly associated with a decreasing risk to develop the SLE; and the smoking was not found to be a protective factor independently associated with the occurrence of SLE (aOR= 2.42; 95% CI= 0.30 - 19.70; p= 0.408) (table 2).

Table 1: Distribution of patients according to the sociodemographic and lifestyle data

Sociodemographic and lifestyle data		Number (N= 43)	Percentage
Sex			
Male		3	6.98
Female		40	93.02
Age group			
< 45 years		38	88.37
≥ 45 years		5	11.63
Lifestyle			
Tobacco	yes	1	2.33
	no	42	97.67
Coffee	yes	11	25.58
	no	32	74.41
Tea	yes	23	53.49
	no	20	46.51
Cola	yes	3	6.98
	no	40	93.02
Alcohol	yes	1	2.33
	no	42	97.67
Drug	yes	1	2.33
	no	43	100.00

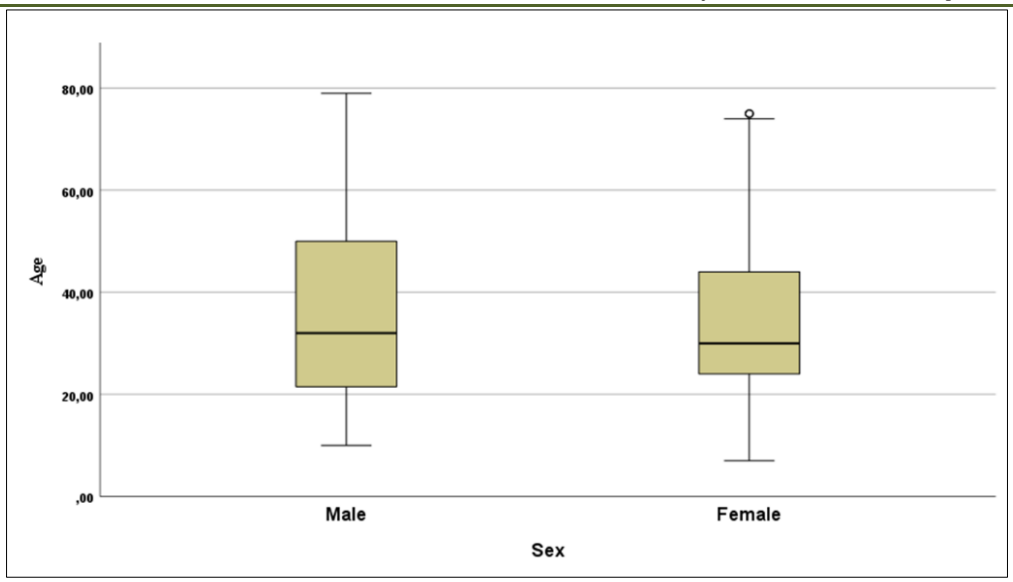

Figure 1: Distribution of patients by the age and the sex.

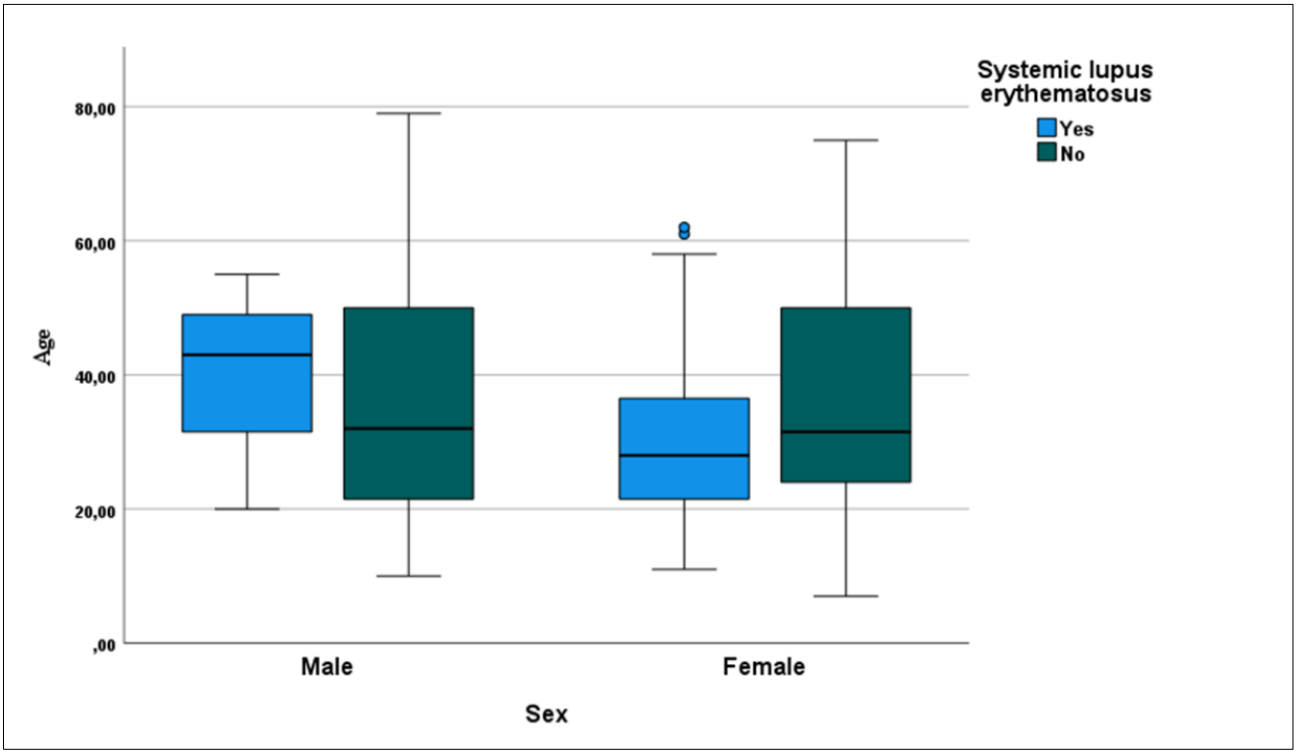

Figure 2: Distribution of lupus patients by the age and the sex.

Table 2: Factors associated with systemic lupus erythematosus Bivariate analysis using binary logistic regression and multivariate analysis using multivariate logistic regression.

Variables[a]		Systemic lupus erythematosus		Crude OR (95% CI)	p	Adjusted OR (95% CI)	p
		Yes, n (%)	No, n (%)				
Sex	Male n (%)	3 (6.98)	108 (39.42)	8.68 (2.62 – 28.74	0.000	8.32 (2.50 – 27.67)	0.001
	Female, n (%)	40 (93.02)	166 (60.58)	1		1	
Age group	< 45 ans, n (%)	38 (88.37)	192 (70.07)	0.31 (0.12 – 0.81)	0.017	0.33 (0.13 – 0.89)	0.028
	≥ 45 ans, n (%)	5 (11.63)	82 (29.93)	1		1	
Tobacco	Yes, n (%)	1 (2.33)	40 (14.60)	7.18 (0.96 – 53.65)	0.055		
	No, n (%)	42 (97.67)	234 (85.40)	1			
Coffee	Yes, n (%)	11 (25.58)	96 (35.04)	1.57 (0.76 – 3.25)	0.226		
	No, n (%)	32 (74.42)	178 (64.96)	1			
Tea	Yes, n (%)	23 (53.49)	146 (53.28)	0.99 (0.52 – 1.89)	0.980		

	No, n (%)	20 (46.51)	128 (46.72)	1			
Cola	Yes, n (%)	3 (6.98)	24 (8.76)	1.28 (0.37 – 4.45)	0.698		
	No, n (%)	43 (93.02)	250 (91.24)	1			
Alcool	Yes, n (%)	1 (2.33)	11 (4.01)	1.76 (0.22 – 13.96)	0.594		
	No, n (%)	42 (97.67)	263 (95.99)	1			
Drug	Yes, n (%)	1 (2.33)	3 (1.09)	0.47 (0.05 – 4.58)	0.512		
	No, n (%)	42 (97.67)	271 (98.91)	1			

OR : odds Ratio **CI** : Confidence intervals

DISCUSSION

Results from this 15-year cross-sectional study revealed that the hospital frequency of SLE is low (0.63%). We found that female remained factors that significantly influenced the development of SLE ; and patients under 45 years were found to be factors that were signicantly associated with a decreasing risk to develop the SLE ; but smoking was not found to be a protective factor independently associated with the occurrence of SLE.

The systemic lupus erythematosus is a chronic inflam matory autoimmune and multi-systemic disease that is characterized by the production of autoantibodies and tissue deposition of immune complexes [7]. Its hospital frequences were estimated at 0,89% [9], and 1 - 2 cases per year [10]. These findings paralel with our study findings.

Previous studies demonstrated the influence of sex-based differences in systemic lupus erythematosus development, in accordance with our study [11, 12].

In our study, the age under 45 years was significantly associated with a decreasing risk to develop the SLE, consistence with previous studies [9, 10].

One patient consumed alcohol in our study. In addition, alcohol consumption was not influence the development of SLE. The result is not consistent with these findings [1-13]. This discrepancy may could be explained by the fact that the lifestyles are extremely between northern society and southern society, particularly in women, which constitute most of study population for autoimmune diseases.

Several studies indicated that the smoking is associated with an increasing risk to develop the SLE, inconsistent with the study conducted in Colombia by Refai *et al*., and our study [14, 1, 13, 6].

Our study has limitations. Firstly, patients hospitalized outside of our study setting and seen in outpatient consultation, which may have led to under-ascertainment on the latter. A second limitation, the lack of some information related to the lifestyle measurement and subjective dimension, which may cause confounding biases. Finally, the study was a single-center study, which may hamper generalizability.

This study contains several strengths. First, it is a long-term observational cross-sectional study that determined some external exposome associated with increasing or decreasing risk to develop the systemic lupus erythematosus. Second, consent procedures were not required for enrollment which may increasing slightly the study sample size. Third, our study demonstrates the scope of the problematic of environmental factors and systemic lupus erythematosus. And finally, our pilot data provide sufficient grounds to more explore the correlation between the three main components of exoposome and systemic lupus erythematosus.

In perspective, a large multicenter cross-sectional study taking into account our study limitations may be crucial in order to identify potential environmental factors associated with SLE and to propose the preventive measures that should be taken to address the environmental risk factors of SLE.

CONCLUSION

Although systemic lupus erythematosus is more common in non-smokers than smokers in our study, suggesting a protective role of smoking, smoking was not found to be an independently associated protective factor for the development of systemic lupus erythematosus. Age over 45 years is significantly associated with a reduced risk of developing systemic lupus erythematosus. Female gender is a factor independently influencing the development of systemic lupus erythematosus.

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