Risk Factors and Predictors of Systemic Lupus Erythematosus: Insights from a Case-Control Study

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ABSTRACT

This study aimed to investigate the risk factors associated with the development of systemic lupus erythematosus (SLE). A total of 72 cases and 142 matched controls were interviewed between 2008 and 2019 at the first clinic of Samarkand State Medical Institute. Clinical data were obtained from the central patient database, and participants meeting more than four SLE criteria were included. The questionnaire addressed variables such as education, body metrics, use of hair dyes, smoking, alcohol consumption, hormonal and endocrine factors, occupational exposure to low temperatures, family history of autoimmune diseases, and psychological stress. The influence of these variables on SLE was analyzed using odds ratios (OR) and 95% confidence intervals (CI). Multivariate analysis revealed that a history of hypertension increased the risk of SLE (OR 3.7, 95% CI 1.36–7.9), and cases were more likely to report angina pectoris compared to controls (OR 4.7, 95% CI 1.6–24). A significant association was found between a family history of autoimmune diseases and SLE risk (OR 2.25, 95% CI 1.25–4.05). Interestingly, alcohol consumption exceeding 200 grams per week was associated with a lower risk of SLE, although the sample size was limited. Smoking 2 to 5 cigarette packs per week increased the risk of SLE (OR 2.64, 95% CI 0.97–7.18), but this finding was not statistically significant. The study concludes that SLE may be linked to both endogenous and exogenous factors, warranting further research to establish causative relationships.

ARTICLE HISTORY
Received 27 November 2024
Accepted 1 January 2025

KEYWORDS: Lupus, SLE, risk factors, smoking, alcohol, stress, family history.

Volume 3 issue 1 (2025)

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by the production of numerous B cells producing hyperactive autoantibodies and involvement of skin, joints, kidneys, brain, serosal surfaces, blood vessels, blood cells, lungs and heart [1]. While genetic and hormonal factors are proved to be significantly important, other risk factors, including different environmental exposure, may have equal importance in the aetiology of SLE. Probably, according to recent research, many different environmental factors may act collectively to cause SLE in a genetically susceptible person [2]. It is hypothesized that some drugs containing aromatic amines have been proposed to cause SLE [3-4]. Therefore, numerous studies investigated environmental agents containing chemical components especially aromatic amines, such as tobacco smoke and hair dyes. The studies that have explored the etiological role of hair dyes in SLE development showed contradictory results [5-6] while smoking tobacco in many studies was associated with an increased risk of SLE [7-9]. In contrast, recent findings demonstrate that alcohol consumption is associated with a decreased risk of SLE [9] with some exceptions [10]. Some other studies suggest that hormone replacement therapy may be associated with an increased risk of SLE [11]. Infectious agents, mainly of viral origin, were also discussed as potential triggers of SLE for many years. [12]. The role of stressful negative life events in the onset of autoimmune diseases is controversial [13]. We undertook a clinic-based case-control study to investigate potential risk factors for developing SLE in the 1st Clinic of Samarkand State Medical Institute.

Materials and methods

Overall, 72 cases and 142 matched controls were interviewed between 2008 and 2019 at the first clinic of Samarkand State Medical Institute. Clinical data for all cases were obtained from the central patients' database of SamMI's 1st Clinic. The diagnosis of SLE was based on American Rheumatism Association's classification criteria. Only those patients who met >4 criteria for SLE were included in the study. For each included case, we matched two controls for sex and age. Controls were randomly selected from the population screening database. Only those who provided informed consent were included in the study.

Socioeconomic, demographic, and clinical factors were compared between cases and controls using the chi-square test for sex and socioeconomic status (categorical variables)

and t-test for age (continuous variable). The proportion of SLE was compared between the entire study sample as well as in age, sex, and socioeconomic status subgroups to avoid confounding effect.

Questionnaire

The questionnaire consisted of questions related to education, body height and weight, hair-dyes (frequency), smoking (number of cigarette packs per week), alcohol consumption (quantity), hormonal/endocrine factors (hormone replacement therapy), occupational exposure to low temperature, a family history of autoimmune diseases and drug allergy, any history of negative psychological events (stress, depression etc.)

Data analysis

The effect of the exposure variables on SLE was measured using the odds ratio (OR) and its 95% confidence interval (CI).

Estimations were performed by conditional logistic regression. In the multivariate analyses, we also tested whether effect modification was present by including relevant interaction terms in the models. For analyses, we used R studio version 3.6.2.

Ethics

The study was approved by the Ethics Committee of Samarkand State Medical Institute.

Results

Smoking, alcohol and body mass index

Our results revealed a negative relationship between higher doses (>200 grams per week) of alcohol consumption and the SLE risk (see Table 1).

Table 1. Conditional logistic regression results (BMI, alcohol, smoking)

Variables	Cases n (%)	Controls n (%)	Odds ratio (OR)	95% CI
Alcohol consumption (grams /week)				
No	32 (44.4)	48 (33.8)	Ref	Ref
>0-200	21 (29.2)	45 (31.7)	0.70	0.35-1.39
>200	19 (26.4)	49 (34.5)	0.49	0.25-0.97
Smoking (packs week)				
0	29 (40.3)	69 (48.6)	Ref	Ref
>0-2	22 (30.6)	45 (31.7)	1.16	0.6-2.27
>2-5	11 (15.3)	19 (13.4)	1.38	0.58-3.26
>5	10 (13.9)	9 (6)	2.64	0.97-7.18
BMI				
<18.5	19 (26.4)	51 (35.9)	1.0	Ref
18.5-24.9	21 (29.2)	48 (33.8)	1.17	0.56-2.45
24.9-29.9	17 (23.6)	29 (20.4)	1.57	0.71-3.49
>30	15 (20.8)	14 (9.8)	2.88	1.17-7.07

The odds ratio was 0.49 for those with alcohol consumption of >200 g/week. There was also a greater risk of SLE among smokers compared to non-smokers (OR = 1.4, 95% CI 0.79-2.49). Those who smoke 2 to 5 cigarette packs per week had 2.64 times increased risk of SLE compared to non-smokers (OR = 2.64, 95% CI 0.97-7.18), however, none of the results on this exposure was statistically significant. Participants who reported alcohol and smoking exposure were males. Only participants with a body mass index (BMI) greater than 30 kg/m2 tended to have a statistically significant greater risk of SLE when compared to those with BMI less than 18.5 kg/m2 (OR = 2.88, 95% CI 1.17-7.07). However, we found no statistically significant dose-response relationship neither among smokers and nor among those overweight and obese.

Family history of autoimmune diseases

Table 2 presents the distribution of autoimmune diseases among close (first degree) relatives and the corresponding odds ratios. There was a statistically significant association between a family history of any autoimmune disease and increased risk of SLE (OR 2.25, 95% CI 1.25-4.05). Especially those with a family history of SLE (OR 3.47, 95% CI 1.21-10) or rheumatoid arthritis (OR 2.7, 95% CI 1.04-7.02) tended to have a significantly greater risk of SLE.

Comorbidities

People with diagnosed hypertension tended to have an increased risk of the development of SLE (OR 3.7, 95% CI 1.36-7.9). Also, cases were more likely to report angina pectoris compared to controls (OR 4.7, 95% CI 1.6-24). Among the infectious diseases, only pneumonia was borderline significantly associated with SLE (OR 1.9, 95% CI 1.0-3.7). A history of blood transfusion had a higher odds ratio (OR 1.8, 95% CI 0.8-3.6) while not statistically significant (see Table 3).

Table 2. Distribution of autoimmune diseases among close relatives of cases and controls with corresponding unadjusted OR and 95% CI

Autoimmune diseases	Cases n (%)	Controls n (%)	OR	95% CI
Any autoimmune disease	35 (48.6)	42 (29.6)	2.25	1.25-4.05
Rheumatoid arthritis	10 (14)	10 (7)	2.7	1.04-7.02
SLE	9 (13)	7 (4.9)	3.47	1.21-10
Multiple sclerosis	4 (5.5)	3 (2.1)	3.6	0.77-16.9
Systemic sclerosis	2 (2.8)	3 (2.1)	1.8	0.29-11.2
Crohn's disease	3 (4.2)	6 (3.5)	1.35	0.32-5.68
Psoriasis	7 (9.7)	20 (14)	0.95	0.37-2.42
Ankylosing spondylitis	3 (4.2)	1 (0.7)	8.1	0.82-80.4
Diabetes Mellitus (I)	2 (2.8)	4 (2.8)	1.35	0.24-7.69

Other variables (hair dyes, occupational exposure to cold)

The hair colouring three or more times per year was not associated with a risk of SLE (OR 1.7, 95% CI 0.86-3.12) compared with less frequent exposure to hair colourants. The proportion of cases who reported occupational exposure to cold was significantly greater among cases rather than controls (32% and 12% respectively, OR 3.44, 95% CI 1.21-9.5). The proportions with close contact with animals (cow, sheep or dog) were 61% of the cases and 39% of the controls (OR 2.31, 95% CI 0.78-6.3). There was a significant association between SLE and exposure to cow (OR 2.8, 95% CI 1.1-5.9). For all four groups of life events classified according to reported by participants information, we observed no association with SLE. However, reported serious accidents tended to have a higher risk of SLE compared to other groups of events (OR 1.7, 95% CI 0.86-3.12).

Table 3. Distribution of comorbidities among cases and controls.

Disease	Cases n (%)	Controls n (%)	OR	95% CI
Immunological diseases				
Asthma	2 (2.8)	8 (5.6)	0.7	0.1-3.1
Multiple sclerosis	2 (2.8)	2(1.4)	3.2	0.8-5.2
Crohn's disease	1 (1.4)	2(1.4)	1.6	0.2-12.1
Psoriasis	3 (4.2)	9 (6.3)	0.7	0.13-2.72
Cardio-vascular diseases				
Myocardial infarction	5 (6.9)	2 (1.4)	2.5	0.43-18
Angina pectoris	6 (8.3)	4 (2.8)	4.7	1.6-24
Stroke	4 (5.5)	2 (1.4)	2.9	0.61-12
Hypertension	32 (44.4)	19 (13.4)	3.7	1.36-7.9
Surgery				
Any surgery	11 (15.3)	20 (10)	1.4	0.6-3.1
Blood transfusion	18 (25)	27 (19)	1.6	0.8-3.6
Infectious diseases				
Herpes zoster	5 (6.9)	12 (8.4)	1.1	0.4-2.9
Pneumonia	21 (29.2)	20.4 (14)	1.7	1.0-3.7
Pyelonephritis	8 (11.1)	15 (10.6)	1.3	0.5-3.2

Discussion

The current point of view on the aetiology of SLE is that several environmental factors act on a genetically predisposed individual to develop or defend against disease. The results of this study suggest that hypertension, family history of autoimmune diseases are risk factors for SLE, and alcohol is a potential protective factor, however, the latter based on weak evidence.

Our data suggest that smoking is associated with an increased risk of SLE, although this did not reach statistical significance. Our results are consistent with previously published results [5-6]. Alcohol consumption has been suggested as a protective factor. In this study, we observed a dose-response relationship between alcohol consumption and SLE, which was even more pronounced in a multivariate model, which further strengthened the observation.

Table 4. Distribution of reported life events among cases and controls

Reported stressors/events	Cases n (%)	Controls n (%)	OR	95% CI
Family (death, divorce, etc.)	14 (11)	22(11)	1.3	0.5-3.6
Financial (any)	3 (1.2)	8 (3.9)	0.4	0.2-3.5
Conflicts (any)	5 (3.7)	13 (6.4)	0.7	0.6-2.6
Accidents (serious)	13(8.5)	16 (7.9)	1.8	0.7-5.7

Thus, our results are consistent with two previous studies that specifically addressed this issue. However, a study conducted by Hardy et al. [9] indicated that data collection was performed from post-diagnostic exposure which may distort the results and are not comparable with the evidence we obtained. Of course, our data may be and likely was influenced by recall bias, but concordance between our evidence and previous studies strongly suggests that the protective effect of alcohol may exist and smokers have a greater risk of developing SLE. We did not observe any indications of an association between hair dyes and SLE.

Among the reported comorbidities investigated, hypertension was associated with a significantly increased risk of SLE. It is also possible, that vascular re-modelling, damage and dysfunction of endothelial cells which contributes to hypertension in SLE could be a primary event, preceding clinical SLE diagnosis [14-15].

Conclusions

Our results do not support several etiological factors including hair dyes, exposure to animals. This could be because too few subjects were investigated, which is the main drawback of this study. Furthermore, the recruitment rate was slightly higher in cases (82%) than in controls (69%) indicating to the possible selection bias. Another source of bias could be recalling the exposure. Cases would probably be more likely to make an effort when filling in the questionnaire. Besides, defining disease onset may be complicated in a disease such as SLE. Notably, we did not find any indications that hormonal factors play any role as risk factors for SLE. However, we did find an indication of a link between animal exposure and the risk of SLE, with exposure to sheep. Negative life events did not show any evidence of a connection. As expected, the most obvious risk factor was a close relative with SLE, which was associated with two times increased risk of SLE. This suggests that environmental and genetic data should be included in future studies.

Acknowledgements

We gratefully acknowledge the help of the Samarkand State Medical University administration for the support on data collection.

Conflict of interest

The authors declared no conflict of interest

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