Research Article

Risk Factors Associated with Systemic Lupus Erythematosus in Oman

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Abstract

Systemic lupus erythematosus is an autoimmune disease with genetic and environmental components. In Oman, it is associated with early age of onset and aggressive presentation. A preliminary case-control study was conducted to identify potential risk factors associated with SLE development. Sixty Omani cases and sixty age- gender- and origin- matched controls participated by filling a questionnaire on demographic information, age of disease onset, family history and exposure to potential environmental factors. Results indicated that 25% of the participated cases have first-degree relatives with the disease (p=1e-4). Sun exposure found to be significantly associated with the disease (p=5e-4) and home incense smoke was suggested as a potential risk factor (p=3e-2). However, a larger size study is required to validate the preliminary findings and investigate the disease associated exposure durations and intensities.

Keywords: Systemic Lupus Erythematosus; Females; Family History; Incense Smoke; Environmental Exposures; Oman

1. Introduction

Systemic lupus erythematous (SLE) is a multisystem autoimmune disease characterized by the production of autoantibodies against cell surface, nuclear and cytoplasmic molecules [1]. Innate and adaptive immune components are involved in the production of autoantibodies and the accumulation of immune complexes, which induce inflammation [2]. In healthy individuals, self-tolerance is controlled by a subset of T helper (Th) cells known as T regulatory (Treg) cells [2].

The generation of Treg is related to an inflammatory Th subset called Th17. In SLE, an increase in the ratio of Th17/Treg was associated with the production of inflammatory cytokines that are associated with B cell activation [2]. First-degree relatives of SLE patients have higher probability of developing SLE or other autoimmune diseases [3-6], which could be due to sharing genetic and/or environmental factors. Some SLE cases are classified as monogenic autosomal recessive disease, but most are polygenic [7]. Several genome-wide association studies (GWAS) showed that polygenic SLE is driven by more than 80 susceptibility loci [8].

The disease heterogeneity and age of disease onset is attributed to differences in the triggering environmental factors and variations in the genetic susceptibility alleles/genes among different races. SLE heterogeneity is influenced by genetic factors (43.9%), shared environmental factors (25.8%) and non-shared environmental factors (30.3%) [3]. Environmental factors thought to trigger the adaptive and innate immune responses by inducing epigenetic changes in genetically susceptible individuals and lead to SLE development [3]. Although there are known SLE environmental risk factors, such as silica, diet, smoking and sun exposure [9], but it remains to clarify the mechanisms by which those factors induce autoimmunity in genetically susceptible individuals. In addition, it remains to find out whether the reported environmental risk factors represent risk for SLE development in other uninvestigated ethnic groups and/or if there are other factors. Better understanding may lead to preventive action and monitoring individuals at risk to detect disease development at early stage.

In Oman, two studies suggested that SLE might be induced by silica exposure and/or sun exposure [10, 11] but this was not investigated. Therefore, we have designed a self-administered questionnaire to detect potential environmental factors associated with SLE in Omani patients compared to age- gender- and origin-matched healthy controls.

2. Methods

2.1 Questionnaire development

A general questionnaire was designed to screen the possible factors that could be associated with SLE. The time required to answer the questionnaire questions did not exceed 15 minutes. The questionnaire included questions (55) on demographic information, family history of autoimmune diseases, and potential environmental risk factors. The survey started with questions on demographics including age, origin, education level, marital status, the age at diagnosis, and family history of autoimmune diseases. The environmental risk factors were assessed by questions on the living area before and after the disease. Occupational exposure was assessed by asking about the working area and relation between working time and disease activity. Silica exposure was associated with the working environment, home area and hobbies like pottery, gardening and Sandboarding or Sand Skiing.

Physical environmental factors were assessed by asking about personal protection when exposed to direct sunlight and working outdoor. In the last part of the survey, questions focused on assessing chemical factors such as, exposure to insecticides, cosmetics, smoking, hair dyes, and the frequency of application in relation to disease. Exposure to insecticides was screened by questions about spraying insecticides around the house, and the frequency of applying them per year. Additionally, questions about application of cosmetics, nail polish, hair dyes, semi-permanent cosmetics and tattoo, and hobbies like painting were asked.

2.2 Ethical approval

Ethical approval for conducting the study was obtained from the ethics committee at the college of medicine and health sciences, Sultan Qaboos University.

2.3 Participants

Participants were categorized into two groups; patients and controls. All patients met ≥ four American College of Rheumatology (ACR) SLE classification criteria and they were recruited randomly by appointment from Sultan Qaboos hospital (SQUH) and. Since we were targeting 18-50 years old patients, females of matching age were invited to participate in the study.

2.4 Survey and data collection

The questionnaire was distributed to people through email, social media and hard copies. Survey questions were in two languages (English and Arabic) to encourage more individuals to participate. The free online tool eSurv was selected to create this survey because it is user friendly and could be easily shared by social media [12]. In addition, it has no limitation on the number of questions and responses and the raw data could be retrieved easily. eSurv is recommended by UK Data Protection Act (DPA) to be used when personal data is to be collected [12].

2.5 Data analysis

Data were exported from eSurv as Tab delimited text and exploratory data analysis was conducted in Microsoft excel. The significant differences between the two groups (patients and controls) were assessed by chi-square or Fisher's exact tests for each variable.

3. Results

3.1 Demographic information

A total of 60 patients and 60 controls participated in the survey. The participants represent most of the regions in the sultanate (Table 1). The majority of cases, 56.7%, are married. A significant difference between cases and controls in education was detected (p=1e-4). About 58% of the cases had education beyond High School compared to about 92% of the controls.

3.2 Age at diagnosis and Family history of SLE

Most of the cases were diagnosed with SLE between 14-29 years (75%). Quarter of the cases (n=15) have first-degree relatives with SLE and the most affected relatives are sisters. Also, 7% and 8% of the cases have second-degree relatives with SLE from the father side or mother side, respectively.

3.3 Environmental risk factors

About 12% of the cases (n=7) recall that the onset of SLE followed an infection. Practices associated with sun exposure, i.e. skin coverage and application of sun block, were significantly different in the surveyed cases compared to controls (Table 4). Data indicated that SLE patients were more exposed to sunlight partially covered compared to controls (p= 5e-4) and that they are less likely to apply sun block during day time (p=1e-2). The use of home incense (locally named Bakhour), which is a major source of indoor smoke, showed suggestive risk (p=3e-2) but smoking and smoky kitchen were not associated. Notably, more cases were living in farms compared to controls (p=3e-2). Use of hair dyes was more in the control group than in cases (p=1e-2). All the other factors including silica exposure were not significantly different.

Variable		Cases n=60 n (%)	Controls n=60 n (%)	p-value
Age	14-19	6 (10.0)	9 (15.0)	0.6
	20-29	19 (31.7)	23 (38.3)	
	30-39	25 (41.7)	22 (36.7)	
	40-49	8 (13.3)	6 (10.0)	
	>50	2 (3.3)	0 (0.0)	
Marital status	Single	24 (40.0)	31 (51.7)	0.27
	Married	34 (56.7)	29 (48.3)	
	Divorced	1 (1.7)	0 (0.0)	
	Widowed	1 (1.7)	0 (0.0)	
Region	Al-Buraimi	0 (0.0)	3 (5)	0.4
	Al-Dakhiliya	17 (28.3)	17 (28.3)	
	Al-Dhahira	4 (6.7)	3 (5.0)	
	Muscat	15 (25)	16 (26.7)	
	North Al-Batina	9 (15.0)	5 (8.3)	
	South Al-Batina	8 (13.3)	13 (21.7)	
	North Al-Sharqiya	5 (8.3)	1 (1.7)	
	South Al-Sharqiya	2 (3.3)	2 (3.3)	
Education	Basic Education or <	2 (3.3)	0 (0.0)	0.0001
	Beyond Basic Education <high school	3 (5.0)	1 (1.7)	
	Vocational	2 (3.3)	0 (0.0)	
	High school	18 (30.0)	4 (6.7)	
	2 years college	6 (10.0)	3 (5.0)	
	Undergraduate student	6 (10.0)	18 (30.0)	
	BSc	19 (31.7)	20 (33.3)	
	MSc	2 (3.3)	11 (18.3)	
	PhD	2 (3.3)	3 (5.0)	
Work	Outdoor- Industrial area	1 (1.7)	0 (0.0)	0.3
	Outdoor - Coastal area	2 (3.3)	0 (0.0)	
	Outdoor - Farm	0 (0.0)	1 (1.7)	
	Mountainous	1 (1.7)	0 (0.0)	
	Desert	1 (1.7)	0 (0.0)	
	Indoor - Well ventilated	23 (38.3)	18 (30.0)	
	Indoor -Poorly ventilated	1 (1.7)	2 (3.3)	
	Not applicable	31 (51.7)	39 (65.0)	

Table 1: Demographic information about the participants.

Age at diagnosis	Count	Percent
<14	8	13.3%
14-19	20	33.3%
20-29	25	41.7%
30-39	3	5.0%
40-49	4	6. 7%

Table 2: Age at disease diagnosis.

The frequency of affected relative						
Relatives degree	**Cases**	**Controls**	**p-value**	**Odds Ratio**	**95% Confidence Intervals**	
First-degree	15 (25.0)	1 (1.7)	0.0001	19.5	2.5	154.5
Second-degree (Father)	4 (6.7)	2 (3.3)	ns	-	-	-
Second-degree (Mother)	4 (8.3)	1 (1.7)	ns	-	-	-
The number of affected relatives						
Relatives degree	**Mother**	**Father**	**Sister**	**Brother**	**Daughter**	**Son**
First-degree	3	-	11	1	-	-
Second-degree (Father)	-	1	1	1	-	1
Second-degree (Mother)	-	-	2	2	1	1

Table 3: Family history of SLE.

Category	**Factor**	**Cases n=60 n (%)**	**Controls n=60 n (%)**	**Odds Ratio**	**95% Confidence Intervals**		**p-value**
					Lower	**Upper**	
Physical exposures	**Sun Block**	30 (50.0)	43 (71.7)	**0.4**	**0.19**	**0.84**	**0.012**
	Skin coverage	47 (78.3)	59 (98.3)	**0.06**	**0.01**	**0.49**	**0.0005**
	Sun protection	12 (20.0)	15 (25.0)	0.75	0.31	1.77	0.33
Chemical exposures	**Arabian Incense**	59 (98.3)	53 (88.3)	**7.79**	**0.92**	**65.43**	**0.031**
	smoky kitchen	1 (1.7)	4 (6.7)	0.24	0.03	2.19	0.182
	Smoking	0 (0.0)	0 (0.0)	-	-	-	-
	Insecticides	39 (78.0)	28 (66.7)	1.77	0.7	4.48	0.163
	Hair dyes	15 (25.0)	28 (46.7)	**0.38**	**0.18**	**0.83**	**0.011**
	Painting	15 (25.0)	15 (25.0)	1	0.44	2.29	0.583

Silica exposure	Desert	1 (1.7)	0 (0.0)	-	-	-	-
	Industrial area	1 (1.7)	0 (0.0)	-	-	-	-
	Sand Surfing	0 (0.0)	1 (1.7)	-	-	-	-
	Farm	8 (13.8)	1 (2.1)	**7.68**	**0.93**	**63.74**	**0.029**
	Gardening	7 (11.7)	4 (6.7)	1.84	0.51	6.68	0.264

Table 4: Selected environmental factors.

4. Discussion

About 58% of the SLE cases achieved education beyond High School compared to about 92% of the controls. Al Maini et al. [11] found that the cases average educational period is 10.8 and thought that this may lead to a socioeconomic disadvantage. We found that most cases develop the disease between 14-29 years. This is consistent with previous studies on Asian populations, which reported that the age onset of SLE is between 19-36 in Asia with lowest reported age from Oman [13]. First-degree relatives with SLE were reported by 25% of SLE cases but about 2% of the controls. This is higher than what previous studies have reported in other populations (1.3-19.4%) [4, 6] but lower than what was reported earlier in Oman [11]. Also, an increase of the second-degree relatives with SLE in cases was reported from the father and mother sides, 7% and 8%, respectively, compared to the controls. This increase could be due to disease increased heritability and/or sharing environmental risk factor. Sisters and mothers were the most reported first-degree relatives with SLE, which may reflect the fact that the disease develops in females more than males during childbearing age.

Sun exposure is one of the environmental triggers for SLE activity. We found a significant difference in practices associated with the level of sun exposure and sun protection, i.e. skin coverage and applying sun block while exposed to direct sunlight, between cases and controls. More controls tend to apply sun block and cover their skin while exposed to sunlight compared to cases. Sunlight exposure is associated with the induction of reactive oxygen species, which leads to DNA damage and the production of autoreactive T cells and autoantibodies [9]. Somers and Richardson [14] found that oxidizing agents can decrease DNMT1 in T helper (Th) cells resulting in demethylation and overexpression of genes in ERK signaling pathway and stimulating the induction of anti-dsDNA antibodies. In support, patients with active SLE found to exhibit reduced DNA methylation and DNMT3A mRNA expression levels in Th cells upon the exposure to UVB [15]. In vitro, UVB catalyzes the formation of a AHR ligand FICZ, which found to interfere with Treg differentiation but drives Th17 differentiation [16].

Beside the environmental factors, lifestyle and cosmetic treatments are possible stimulators of disease activity. Hair dyes are one of the major widely used among females in most countries. They have been studied to know their influence epidemiologically and immunologically in regards to SLE because they contain aromatic amines that are known to induce SLE-like symptoms [17]. Earlier studies have excluded hair dyes as a possible trigger for SLE. However, our results, indicated association with controls.

Most of the epidemiological studies in SLE focused on cigarette smoking and only few have evaluated the potential association with air pollution. A meta-analysis

published in 2015, showed that smoking is a risk factor for SLE based on 13 studies, respectively. Smoking thought to modify DNA and increase its release through apoptosis, NETosis and necrosis, which trigger loss of tolerance and leads to the production of autoantibodies against DNA. An additional possible explanation is that smoke is associated with survivin, an antigen presentation enhancer and apoptosis inhibitor that may maintains the survival and proliferation of autoreactive B an T cells [18]. In addition, some studies showed the effect of cigarette smoke on reducing the level of anti-inflammatory cytokines and increasing the production of pro-inflammatory cytokines [9]. Smoke active compounds (such as tars, PAHs, and free radicals) found to increase oxidative stress, which cause DNA damage and associated with SLE development [9].

In Oman, cigarette smoking is not common especially among females and therefore in addition to cigarette smoking, we also investigated other sources of smoke as potential risk factors. As we expected none of the cases nor the controls were smokers and/or were exposed to cigarette smoke. However, more SLE cases (n=59, 98%) found to use home incense (Bakhour) compared to controls. Although this is suggestive of a potential significant environmental trigger, but the wide confidence intervals highlighted that the sample size was too small. Bakhour is the main source of indoor smoke in Oman and other Asian countries. An earlier study from Oman associated Bakhour with worsening of wheeze in asthmatic children [19].

A study by Dalibalta et al. [20] showed that incense burning is a significant source of indoor air pollution. Smoke contains more than 800 compounds, 42 are suspected/known carcinogens, 20 toxic compounds, and at least 200 known irritants to the eye, skin, respiratory and digestive tracts. Comparing the smoke generated from a cigarette to the smoke generated from burning home incense show common chemical compounds such as Carbon monoxide, nitrogen dioxide, benzene, toluene, isoprene, formaldehyde, acetaldehyde and naphthalene [20, 21]. In addition, Bakhour is made of woodchips soaked in scented oils, and recently wood smoke shown to enhance Th17 differentiation at lower concentrations than Motor oil [22]. Although we did not detect an association between SLE and silica exposure from question on desert, industrial areas, sand associated activities, however, results showed an increase of SLE cases living and/or working in farms. This may be due to a significant exposure but to lower levels of silica or it may associate with pesticide exposure, which is another potential risk factor for SLE [23].

5. Conclusion

This study indicated potential risk factors associated with SLE in Omani cases. However, questions on duration as well intensity of exposure to the identified environmental factors and increasing the sample size is required to validate the observed results.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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