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Cigarette smoking and risk of primary systemic vasculitis: a propensity score matching analysis

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Abstract. *Introduction:* Considering limited data about the association between smoking and primary systemic vasculitides (PSV), present study aims to investigate smoking habit in PSV patients compared to healthy subjects as well as to examine the effect of smoking on clinical characteristics, disease activity and disease outcome in PSV patients. *Methodology:* We included 126 patients diagnosed with PSV and 210 age- and sex-matched healthy controls. Demographic and clinical information and smoking history of patients and healthy controls were obtained by direct interview and questionnaire. Individuals who had smoked at least 100 cigarettes in their lifetime before the first symptom of vasculitis were classified as smokers; those who had never smoked or smoked less than 100 cigarettes in their lifetime were categorized as never smokers. Disease activity was evaluated by Birmingham Vasculitis Activity Score (BVAS). Disease outcome was assessed by vasculitis damage index (VDI) and the number of patients with disease in remission. Propensity score matching analyses (PSM) for reducing the heterogeneity between studied groups and calculating the actual effect of smoking in PSV was performed. *Results:* No significant differences were observed in clinical manifestations and disease outcome of patients including VDI and the patients with disease in remission between ever and never smokers. However, disease activity according to BVAS in ever smokers was significantly higher than never smokers (P=0.020). PSM resulted in 82 patients with PSV, and 164 matched healthy persons with similar baseline characteristics. By multivariate logistic regression and after adjustment for age, sex, marital status and educational status, ever smoking was not significantly associated with an increased risk of PSV compared with never smoking. *Discussion and conclusion:* Our study indicated a significant association between disease activity and smoking as well as a non-significant association between the clinical manifestations and disease outcome of PSV with smoking in Azeri population. Although further studies are needed to confirm these preliminary results, it seems that smoking may not be a significant risk factor for PSV. *(Sarcoidosis Vasc Diffuse Lung Dis 2019; 36 (3): 243-250)*

Key words: smoking, primary systemic vasculitis, risk factors, propensity score matching

Introduction

Primary systemic vasculitides (PSV) are a heterogenous group of disorders in which inflammation in blood vessel walls develops and leads to mural structures damage and tissue ischemia without a known cause. PSV are relatively uncommon disorders, with annual incidence of 40 to 54 cases per 1 million persons (1). Although pathogenesis of PSV is not completely known, main mechanisms of vascular damage are immune complex deposition, anti-neutrophilic cytoplasmic antibodies (ANCA) (humoral response), and T-lymphocyte response with granuloma formation (cell-mediated) which result in endothelial cell activation, vessel obstruction and dependent tissue

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ischemia (2, 3). Smoking is one of the environmental factors that have an important role in the genesis of aberrant immune response and development of numerous inflammatory diseases (4). Smoking is a well-established risk factor for rheumatoid arthritis (RA), systemic lupus erythematous (SLE), Graves' disease and multiple sclerosis and has also been associated with phenotypic variations in ankylosing spondylitis (5-8). Smoking is also associated with more intensive disease course in inflammatory diseases (8). Ghaussy et al. (9) found significantly higher SLE disease activity index (SLEDAI) in smokers compared to non-smokers. Smoking affects both innate and adaptive immune systems and plays dual roles in modulating immunity by either exacerbation of pathogenic immune responses or weakening of defensive immunity (4). Some proposed mechanisms for the role of smoking in autoimmune diseases pathogenesis are: a) promotion of vascular inflammation by increasing of neutrophil chemotaxis and recruitment of polymorphonuclears, monocytes and macrophages, release of H_2O_2, activation of nuclear factor-κB (NF-κB) and up-regulation of interlukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α) (10-15); b) increasing IL-17 expression in the airway mucosa (16); c) increasing proteinase 3 expression by the endothelial cells (17); endothelial cells dysfunction, i.e. alteration in NO dependent vasodilation (18) and increase in endothelin-1 (ET-1) (19); d) inducing Survivin expression (20). Survivin is a multifunctional protein that is required for growth and differentiation of cells (20). Survivin triggers aberrant immune response by increasing of antigen presentation, prevention of autoreactive cells apoptosis and supporting synthesis of autoantibodies (21).

Data on the role of smoking in vasculitis are rare and limited to the subset of Behcet's disease (BD) (22-26), rheumatoid vasculitis (27, 28) and ANCA associated small vessel vasculitis (29-32). According to Turesson et al. (27) study, smoking is an independent risk factor for vasculitis and other types of severe extra articular RA. However, another study reports a lower proportion of active smokers in patients with ANCA associated small vessel vasculitis in comparison with the entire population of Germany (29). In addition, some studies report a positive relationship between smoking and the clinical features of BD (22, 23). However, other studies demonstrate that patients with BD have fewer oral aphthous ulcers (both in number and frequency) during periods of smoking compared to periods of abstinence (24-26). Since there are limited data about the assosciation between smoking and PVS, present study aims to investigate smoking habit in PSV patients compared with healthy subjects, as well as to examine the effect of smoking on clinical characteristics, disease activity and disease outcome in patients with PSV.

Methods and materials

Study design, patient sample, and data collection

This case-control study was conducted from October 2017 to April 2018 at the Connective Tissue Diseases Research Center (CTDRC). We included 126 patients diagnosed with PVS and 210 age- and sex-matched healthy controls. Patients older than 16 years of age who met either the American College of Rheumatology (ACR) 1990 classification criteria (33) or 2012 Chapel Hill Consensus Conference (CHCC) definition (34) for Takayasu arteritis (TAK), giant cell arteritis (GCA), polymyalgia rheumatica (PMR), polyarteritis nodosa (PAN), granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome), IgA vasculitis (IgAV, formerly Henoch-Schönlein purpura), hypocomplementemic urticarial vasculitis (HUV), cutaneous small-vessel vasculitis and central nervous system vasculitis (CNSV) consecutively, were recruited from the outpatient vasculitis clinic of CTDRC. Microscopic polyangiitis (MPA) was an exception because no ACR classification criteria were available. MPA cases were included if they met the 2012 CHCC definition. Because of diversity in the pathogenesis and clinical characteristics of PSV, we divided them to four groups of large vessel vasculitis including GCA, PMR and TAK; ANCA associated vasculitis including GPA, EGPA and MPA; immune complex small vessel vasculitis and cutaneous LCV including IgAV, HUS and CNSV; and medium vessel vasculitis (PAN and undifferentiated vasculitis with medium vessel involvement).

Detailed demographic and clinical information and smoking history of patients and healthy controls were obtained by direct interview and questionnaire. Smoking status was self-reported based on the fol-

lowing questions: 1. Have you ever smoked cigarettes? and 2. Do you smoke cigarettes now?. Those individuals who reported smoking were asked to report the total number of years smoked, and how many cigarettes and packs of cigarettes they smoked per day. They were then classified into the following groups based on their responses to the questions: individuals who had smoked at least 100 cigarettes in their lifetime before the first symptom of vasculitis, were classified as smokers; those who had never smoked or smoked less than 100 cigarettes in their lifetime, were categorized as never smokers; individuals who indicated they had smoked and were currently smoking, were classified as current smokers; and those who reported smoking but did not smoke at the time of data collection, were classified as past smokers. Current and past smokers were classified together as ever smokers for the purposes of this analysis. In case of smokers, smoking duration based on years and the number of smoked cigarettes per day were recorded. Pack-years were calculated as number of packs smoked per day multiplied by the number of years smoked. Patients' ages at the time of disease onset were included in this analysis. The controls were matched to the age that PSV cases had been when they first experienced a symptom referable to vasculitis. The vasculitis duration was calculated from the first symptom attributable to vasculitis. Disease activity at the time of disease diagnosis was measured by Birmingham Vasculitis Activity Score version of 3 (BVAS v.3) (35). Disease outcome at the time of disease diagnosis and in the last visit was assessed by vasculitis damage index (VDI) (36) and the number of patients with disease in remission.

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (TUOMS) and performed according to the Helsinki humanity research declaration (2008). Furthermore, written informed consent was obtained from all the participants. During the study, all the personal information was kept confidential and other ethical and humanitarian considerations were performed accordingly.

Statistical analysis

Statistical analyses were performed using the SPSS statistical package (SPSS Inc., version 22). Variables were displayed as numbers (percentages), means ± SD or median (Min-Max), as appropriate. Between group comparisons were made by Chi-squared test, Independent-sample t test, or Mann–Whitney U test, as appropriate. Propensity score matching (PSM) analyses for reducing the heterogeneity between studied groups and calculating the actual effect of smoking in PSV was performed. Matching was performed based on demographic characteristics (age, gender, educational status and marital status). For each case with PSV, two healthy persons were selected as the control groups (ratio 2:1). Finally, 82 persons with PSV and 164 healthy unrelated persons analyzed. After propensity score matching, we carried out multivariate analyses with BD as the main outcome variable and smoking history as the main predictor variable to calculate odds ratios with 95% confidence intervals (OR, 95% CI). *P*-value less than 0.05 was considered significant.

Results

One hundred and twenty-six patients with PSV and 214 healthy individuals were enrolled for the purpose of the present study. No significant difference was observed in demographic characteristics of case and control groups (Table 1). PMR/GCA and GPA were the most common type of PSV (Table 2). Constitutional, cutaneous, renal and nervous system symptoms were the most common manifestations of PSV in the studied patients (Table 2). The smoking prevalence (including both past and current smokers) in the PSV group was 21.4% as compared to a 19.5% prevalence in the control group. Difference was not significant. There was no significant difference in the frequency of smoking in the four groups of PSV (Table 3). We compared demographic and clinical characteristics of ever and never smoker PSV patients (Table 4). Ever smokers were older than never smokers. Males were significantly more ever smoker. No significant differences were observed in clinical manifestations of PSV between ever and never smokers. Furthermore, no significant differences were observed in disease outcome of PSV including VDI and the patients with disease in remission between ever and never smokers. However, disease activity according to BVAS in ever smokers was significantly higher than never smokers. No correlation was observed between higher pack years and BVAS (r=-0.181, P=0.386).

Table 1. Demographic characteristics and smoking status of participants

Variables	Patient group (n=126)	Control group (n=210)	*P**
Age (years)	48.67±16.5	49.35±15.3	0.703
Gender			0.296
Female	70 (55.6)	112 (53.3)	
Male	56 (44.4)	98 (46.7)	
Education			0.725
Illiterate	34 (27.0)	51 (24.3)	
Primary school	43 (34.1)	77 (36.7)	
High school	25 (19.8)	45 (21.4)	
University	24 (19.0)	37 (17.6)	
Marital status			0.567
Single	47 (37.3)	71 (33.8)	
Married	79 (62.7)	139 (66.2)	
Smoking status			0.911
Never-smoker	99 (78.6)	169 (80.5)	
Current smokers	22 (17.5)	33 (15.7)	
Past smokers	5 (3.9)	8 (3.8)	
Ever smokers	27 (21.4)	41 (19.5)	
Pack-years of smoking	33.49±15.8	24.21±14.9	0.148

Categorical and quantitative variables were displayed as numbers (percentages) and means ± SD, respectively.
$P < 0.05$ was considered significant.
* *P* values indicate comparison between groups (Independent-sample t test or Chi squared, as appropriate).

Table 2. Clinical characteristics of vasculitis group

Variables	Number (n=126)	Percent
Types of vasculitis		
Polymyalgia rheumatica/giant cell arteritis	28	22.2
Granulomatosis with polyangiitis	26	20.6
Cutaneous small-vessel vasculitis	15	11.9
Undifferentiated vasculitis	15	11.9
Takayasu arteritis	12	9.5
Polyarteritis nodosa	10	7.9
Eosinophilic granulomatosis with polyangiitis	6	4.8
Hypocomplementemic urticarial vasculitis	5	4.0
IgA vasculitis	4	3.2
Microscopic Polyangiitis	4	3.2
Central nervous system vasculitis	1	0.8
Disease duration (months)	37.72±18.1	-
Clinical manifestations		
General symptoms	74	58.7
Cutaneous and mucous membranes involvement	57	45.2
Ophthalmic involvement	10	7.9
Ears, nose and throat involvement	26	20.6
Pulmonary involvement	25	19.8
Cardiovascular system involvement	19	15.1
Abdominal involvement	6	4.8
Renal involvement	40	31.7
Nervous System involvement	41	32.5
BVAS	10.6 (1-36)	-

BVAS: Birmingham Vasculitis Activity Score.
Data were displayed as numbers (percentages), means ± SD or median (Min-Max), as appropriate

Table 3. Smoking status in different groups of PSV in comparison with control group

Variables	Smokers (%)	*P*
PSV group		
ANCA associated vasculitis	11 (30.6)	0.617
Large vessel vasculitis	7 (17.5)	
Immune complex small vessel vasculitis and cutaneous LCV	4 (16.7)	
Medium vessel vasculitis (PAN and others)	5 (20)	
Control group	41 (19.5)	

PSV: primary systemic vasculitides;
Data were displayed as numbers (percentages).
* *P* values indicate comparison between groups (Chi squared).

Table 4. Comparison of demographic and clinical characteristics of PSV patients between ever and never smokers

Variables	Ever smokers (N=27)	Never smokers (N=99)	*P*
Age	54.85±13.9	46.99±16.8	0.028
Sex (Female/Male)	3/24	67/32	0.0001
General symptoms (%)	19 (70.4)	55 (55.6)	0.128
Cutaneous involvement/Mucous membranes (%)	12 (44.4)	45 (45.6)	0.517
Ophthalmic involvement (%)	3 (11.1)	7 (7.1)	0.356
Ears, nose, throat involvement (%)	9 (33.3)	17 (17.1)	0.068
Pulmonary involvement (%)	8 (29.6)	17 (17.2)	0.123
Cardiovascular system involvement (%)	4 (14.8)	15 (15.2)	0.602
Abdominal involvement (%)	2 (7.4)	4 (4.0)	0.389
Renal involvement (%)	11 (40.7)	29 (29.3)	0.201
Nervous system involvement (%)	9 (33.3)	32 (32.3)	0.147
BVAS at the baseline	13.96±8.9	9.69±5.8	0.020
VDI at the baseline	0 (0-3)	0 (0-3)	0.632
VDI at the last visit	0 (0-3)	1 (0-4)	0.595
Patients with disease in remission	23 (33.3)	89 (35.5)	0.540

PSV: primary systemic vasculitides; BVAS: Birmingham Vasculitis Activity Score; VDI: Vasculitis Damage Index.
Data were displayed as numbers (percentages), means ± SD, or median (Min-Max), as appropriate.
P< 0.05 was considered significant.
* *P* values indicate comparison between groups (Chi squared, Independent-sample t test or Mann–Whitney U test, as appropriate)

PSM resulted in 82 patients with PSV, and 164 matched healthy persons with similar baseline characteristics (Table 5). By multivariate logistic regression and after adjustment for age, sex, marital status, educational status and smoking status, ever smoking was not significantly associated with an increased risk of PSV compared with never smoking (Table 6).

Discussion

We performed a case-control study of smoking status among PSV patients and healthy controls. Based on our study, there was no significant difference in smoking status between PSV patients and healthy control group. Furthermore, there was no significant difference in clinical manifestations of PSV as well as disease outcome between ever smokers and never smokers.

There is little information about the risk of vasculitis and smoking. Similar to our study, Lane et al. (32) in a case control study on 74 patients with ANCA associated vasculitis could not find any significant difference in the prevalence of smoking in the vasculitis and control groups. Sessa et al. (31) in a study on 28 patients with ANCA-associated idiopathic systemic vasculitis all of whom had rapidly progressive renal failure, reported that 71% of their non-elderly patients (younger than 59) were heavy smokers which was not consistent with present study. Their study had no control group. They proposed that smoking had deleterious effect on the endothelium of the glomeruli and the renal micro vessels. Also, in a retrospective cohort study, Yamaguchi et al. (30) showed that

Table 5. Demographic characteristics of participants post propensity score matching

Variables	PSV group (n=82)	Control group (n=164)	*P*
Age (years)	46.5±14.2	47.2±11.1	0.711
Gender			0.916
Female	44 (53.4)	93 (56.7)	
Male	38 (46.3)	71 (43.3)	
Education			0.973
Illiterate (%)	25 (30.5)	48 (29.3)	
Primary school (%)	22 (26.8)	45 (27.4)	
High school (%)	18 (22.0)	35 (21.3)	
University (%)	17 (20.7)	37 (22.6)	
Marital status			0.973
Single (%)	29 (34.5)	55 (33.5)	
Married (%)	53 (63.1)	109 (66.5)	
Smoking status			0.904
Never-smoker	63 (75.8)	129 (77.5)	
Ever smokers	20 (23.2)	37 (22.5)	

PSV: primary systemic vasculitides.
Categorical and quantitative variables were displayed as numbers (percentages) and means ± SD, respectively.
P< 0.05 was considered significant.
* *P* values indicate comparison between groups (Independent-sample t test or Chi squared, as appropriate).

Table 6. Multivariate analysis of the association between smoking and PSV post propensity score matching

Variables	OR	95% CI for OR		Sig
		Lower	Upper	
Age (years)	1.005	0.978	1.034	0.713
Gender				
Female	-	-	-	-
Male	0.929	0.479	1.803	0.828
Education				
Illiterate (%)	-	-	-	-
Primary school (%)	0.856	0.328	2.236	0.750
High school (%)	0.985	0.417	2.324	0.973
University (%)	1.152	0.503	2.640	0.738
Marital status				
Married (%)	-	-	-	-
Single (%)	0.887	0.427	1.842	0.747
Smoking status				
Never-smoker	-	-	-	-
Ever smokers	1.063	0.481	2.346	0.880

PSV: primary systemic vasculitides; CI: confidence interval; OR: odds ratio.

smoking was a significant and dose-dependent risk factor for relapse of microscopic polyangiitis (MPA) in Japanese patients (hazard ratio, 7.48; 95% confidence interval, 2.73–21.0). Furthermore, Turesson et al. (27) who reported that smoking was an independent risk factor for vasculitis and other types of severe extra articular RA. In a case control study on 86 RA patients with vasculitis and 172 RA patients without vasculitis, Makol et al. (28) showed that smoking was a risk factor for rheumatoid vasculitis with the odd ratio of 1.98 (CI: 1.10-3.56). In Haubitz et al. (29) study on 197 patients with ANCA associated vas-

culitis in Germany, 14% of patients were smokers at the time of the first disease manifestation, which was significantly lower than the prevalence of smoking in the general German population (24.3% smokers). This difference was seen for both men and women, separately. They proposed that smoking was an environmental factor, which decreased the risk of ANCA associated vasculitis.

Our study did not show any association between smoking and organ involvement. Similarly, Hubitz et al. (29) study did not show any significant difference between smokers, non-smokers, or ex-smokers in disease manifestations, mortality, and development of end stage renal disease and relapse rate of ANCA associated small vessel vasculitis. Furthermore, no significant differences were observed in the clinical manifestations of BD patients in ever smokers and never smokers (37). However, disease activity in ever smokers at disease presentation was significantly more than never smokers (37) which was consistent with present study. Gür et al. (38) in a study on BD patients did not report any association between smoking and articular involvement. Moreover, Bilgin et al. (39) could not show any association between smoking and localization of inflammation in eye, duration and frequency of uveitis attacks in BD. In contrast, Lee et al. (22) showed that the frequency of vascular and gastrointestinal lesions in smokers was significantly more than non-smokers with BD. Another study on patients with BD showed a strong association between smoking with severity of disease and organ involvement (25). In another study, Krause et al. (40) reported that in 3 out of 12 smoker BD patients, smoking exacerbated the oral aphthous ulcers. Discrepancy between various studies might be due to differences in studied population, disease duration, and baseline disease activity as well as type, dosage and duration of medical therapies. Further studies would be required to clarify if and how smoking correlates with clinical parameters in PSV.

The limitations of the present study included the relatively small sample size and that information about the smoking status of the participants was obtained retrospectively and might have changed with the onset of vasculitis. The strengths of our study were the case-control design and the belonging of the patients to a single ethnicity; that was Azeri.

In conclusion, the results of present study indicated a significant association between disease activity and smoking as well as a non-significant association between the clinical manifestations and disease outcome of PSV with smoking in Azeri population. Although further studies are needed to confirm these preliminary results, it seems that smoking may not be a significant risk factor for PSV.

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