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A preliminary study of association of cigarette smoking with risk of neuromyelitis optica spectrum disorder

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Abstract

Various studies have revealed an association between cigarette smoking and increased risk for multiple sclerosis (MS). However, its role in neuromyelitis optica spectrum disorder (NMOSD) remains elusive. Therefore, in the present case-control study, we aimed to assess the association of active and passive cigarette smoking with the risk of MS and NMOSD.

Thirty-six patients with NMOSD, 46 patients with MS, and 122 healthy individuals were included in this study. Standardized questionnaires and telephone interviews were used to collect information regarding the active and passive cigarette smoking behaviors of the patients and normal controls.

The risk of MS was significantly higher among smokers than among nonsmokers (odds ratio = 2.166, 95% confidence interval: 1.109–4.170; P = .027). Further analysis of the risk between active and passive smokers, male smokers and nonsmokers showed no statistical difference. However, neither smokers nor active smokers had a greater or lower risk of NMOSD than their nonsmoking counterparts.

Our preliminary study showed no significant association between cigarette smoking and the risk of NMOSD, strongly suggesting that, unlike MS, cigarette smoking might not confer NMOSD susceptibility, at least in the Northern Han Chinese population.

Abbreviations: AQP-4 = aquaporin-4, CNS = central nervous system, MS = multiple sclerosis, NCs = normal controls, NMO = neuromyelitis optica, NMOSD = neuromyelitis optica spectrum disorder.

Keywords: multiple sclerosis, neuromyelitis optica spectrum disorder, risk, smoking

1. Introduction

Neuromyelitis optica (NMO), an inflammatory demyelinating disease of the central nervous system (CNS), has long been considered a variant of multiple sclerosis (MS). However, after the discovery of a highly specific serum autoantibody NMO-IgG targeting water channel aquaporin-4 (AQP4), NMO is now generally believed to be a unique disease entity distinct from MS.[1,2] Based on more observations of serum AQP4-IgG detected in patients with limited forms of NMO (longitudinal extensive transverse myelitis, recurrent optic neuritis) or with otherwise typical CNS lesions (cerebral, diencephalic, and brainstem), the term NMO spectrum disorder (NMOSD) was introduced by Wingerchuk et al in 2007.[3] In 2015, the International Panel for NMO Diagnosis (IPND) proposed new diagnostic criteria for NMOSD, which was stratified using serologic tests (NMOSD with or without AQP-4 antibody).[4]

Unlike MS, little is known about the risk factors for NMOSD, as few studies have been performed on adult and pediatric NMOSD. A pediatric study showed that breastfeeding and daycare exposure may be the 2 early protective factors against the development of NMO,[5] while an adult study revealed no evidence of an association between MS-related risk factors (including a history of infectious mononucleosis, anti-EBNA1 antibody titers, and HLA-DR15) and susceptibility to NMO or transverse myelitis.[6]

Among the risk factors, cigarette smoking has attracted more attention as it is associated with numerous autoimmune diseases by regulating both innate and adaptive immunity.[7,8] As a relatively modern habit, cigarette smoking is prevalent worldwide with approximately one-third of the adult population being smokers. Exposure to tobacco smoking has been regarded as a crucial cause of preventable death worldwide[9] and is involved in a variety of diseases, including respiratory, cardiovascular, and neurological diseases, as well as pregnancy outcome, graft

rejection, and cancers.[8] Various studies have indicated that cigarette smoking is associated with susceptibility, disease progression, and neurological disability in MS.[10–14] However, it remains uncertain whether cigarette smoking confers risk of NMOSD. Hence, to determine the impact of smoking on NMOSD risk in the Northern Han Chinese population, we conducted a preliminary study to investigate the association of smoking with NMOSD odds using a questionnaire method.

2. Patients and methods

2.1. Patients and controls

The study was a cross-sectional analysis of 215 individuals (Fig. 1) recruited at Peking University People's Hospital and Beijing Anzhen Hospital between January 01, 2017 and December 12, 2019. Seventy patients with NMOSD (24 men and 46 women; median age, 44 years; range, 10–86 years) were enrolled in this study. All the patients undertook detection of serum NMO-IgG via an anti-AQP4 Ab assay on an anti-AQP4-transfected cell line using a commercial BIOCHIP kit (Euroimmun, Lübeck, Germany) and met the 2015 IPND criteria.[4] Sixty patients with MS (16 men and 44 women; median age 38 years, range 18–79 years) who met the revised McDonald criteria of 2017 were included.[15] One hundred twenty-six healthy volunteers (39 men and 87 women; median age, 31 years; range, 20–68 years) were recruited as age- and sex-matched normal controls (NCs). All participants answered the questionnaires by themselves and signed the written informed consent before the start of the study, which was approved by the Ethical Committee of Beijing Anzhen Hospital. Almost all participants were Chinese and residing in the northern part of China.

2.2. Questionnaire on smoking habit

To assess the possible association between cigarette smoking and the risk of MS and NMOSD, a researcher-made questionnaire (part of smoking habit, provided in the Supplemental Digital Content, http://links.lww.com/MD2/A422, http://links.lww.com/MD2/A423) was designed and comprised patients' demographic information, present, and past lifestyles, clinical characteristics, medical history, and lifetime information of smoking habits, which covers lifetime cigarette smoking status, daily or cumulative smoking amount, and duration of smoking. Experienced interviewers conducted face-to-face interviews to collect relevant data. The patients' lifetime smoking status was classified into the following 3 categories: nonsmokers (never smoke or exposed to environmental smoke), ever-smokers (smoked in their lifetime and currently a nonsmoker), and current smokers (smoked in their lifetime and currently a smoker). Additionally, smokers were subdivided into active and passive smokers; the former was referred to as a person who currently smoked a minimum of 1 pack of cigarettes per day, while the latter represented a person who lived with a regularly smoking person or had been with a regular smoker in the workplace.
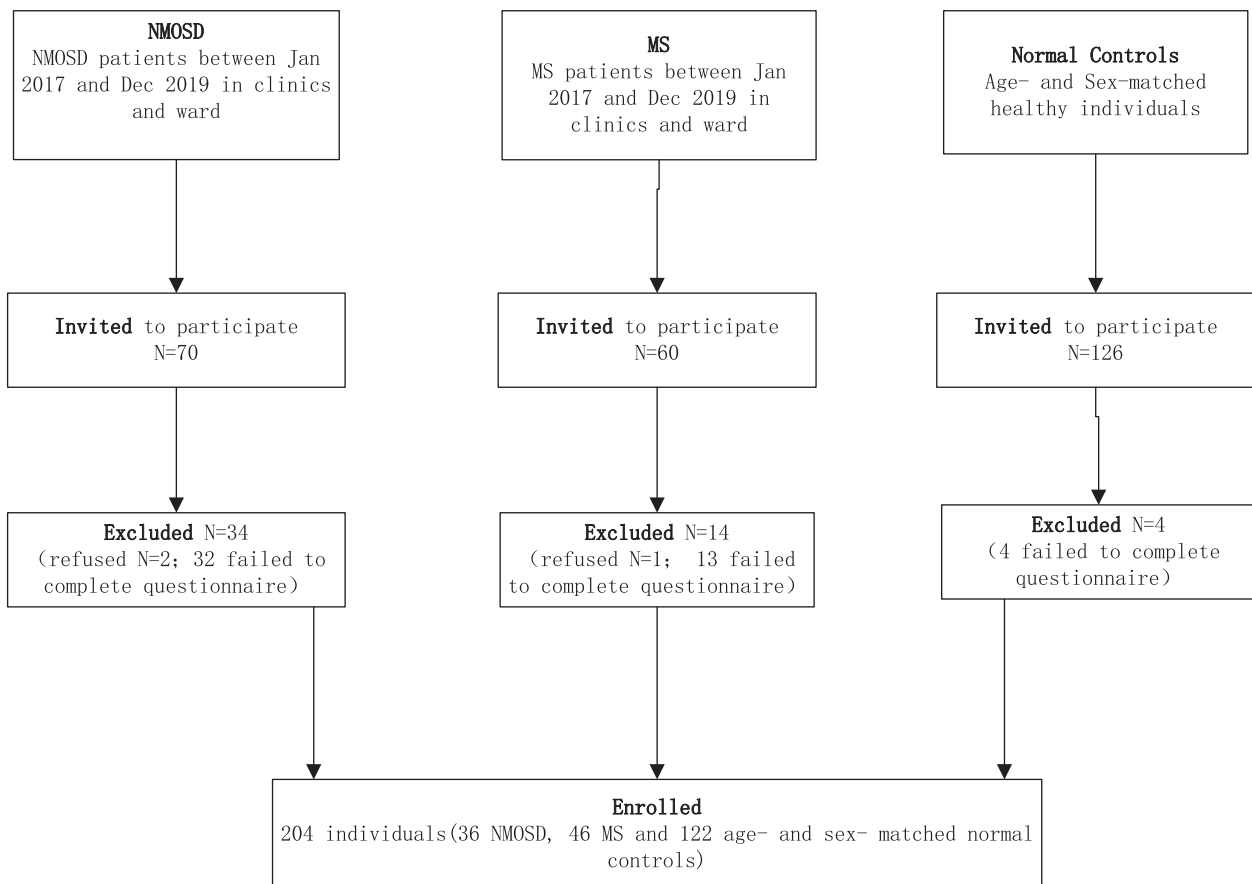
Figure 1. Flow chart describing the enrollment of patients with neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS) and normal controls.

Table 1

Demographics of all participants.

Characteristics	NMOSD (N = 36) n (%)	MS (N = 46) n (%)	NCs (N = 122) n (%)	P-value
Current age (years)				
Median (range)	52 (10,86)	37.5 (22,79)	30 (20,59)	<.01
Age (yr) at onset	49 (10, 85)	34.5 (20, 79)		.05
Median (range)				
Body mass index, mean±SD	22.99±3.32	22.61±3.66	22.66±3.10	.847
Sex				.312
Male	15 (41.7%)	12 (26.1%)	38 (31.1%)	
Female	21 (58.3%)	34 (73.9%)	84 (68.9%)	
Disease duration (mo)	6.5 (0.1, 336)	6.5 (0.1, 168)		.854
Median (range)				
EDSS score, Median (range)	3.75 (0.5, 9.5)	2.5 (1, 7.5)		.011
Area				.641
Northern	36 (100%)	45 (97.8%)	119 (97.5%)	
Southern	0	1 (2.2%)	3 (2.5%)	
Area of birth				.758
Northern	33 (91.7%)	40 (87.0%)	110 (90.2%)	
Southern	3 (8.3%)	6 (13.0%)	12 (9.8%)	

EDSS = expanded Disability Status Scale, MS = multiple sclerosis, NCs = normal controls, NMOSD = neuromyelitis optica spectrum disorder.

2.3. General information

Height, body weight, birthplace, current place of residence, and outdoor activity time were also included in the questionnaires. Age at MS or NMOSD onset and disability measured by the Kurtzke Expanded Disability Status Scale were collected from medical records.

2.4. Statistical analysis

Statistical analysis was performed using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA). Data are presented as the mean± standard deviation or median with range (age). Normally distributed data were processed using one-way analysis of variance and Student–Newman–Keuls posthoc test. Non-normally distributed data were analyzed using Kruskal–Wallis one-way analysis of variance. Categorical variables were presented as frequencies and percentages (nonsmokers, ever-smokers, and current-smokers; active smokers and passive smokers) and were compared using the chi-square test. Statistical significance was set at $P \leq .05$, and values of $P \leq .01$ were considered highly statistically significant.

3. Results

3.1. Participant demographics

The demographic features of the patients with MS, NMOSD, and NCs are shown in Table 1. Two hundred and four valid questionnaires or telephonic interviews with 36 patients with NMOSD (15 men and 21 women; median age 52 years, range 10–86 years), 46 patients with MS (12 men and 34 women; median age 37.5 years, range 22–79 years) and 122 healthy volunteers (38 men and 84 women; median age 30 years, ranged 20–59 years) were obtained. The median Kurtzke Expanded Disability Status Scale scores of the NMOSD and MS groups were 3.75 and 2.5, respectively. The median disease duration of NMOSD and MS was 6.5 and 6.5 months, respectively.

3.2. Association of smoking with risk of MS and NMOSD

The risk of MS increased significantly among smokers compared with nonsmokers (odds ratio [OR] = 2.166, 95% confidence interval [CI]: 1.109–4.170; $P = .027$) (Table 2). Further analysis of the risk between male smokers and nonsmokers, active and passive smokers showed no statistical difference (Tables 3 and 4). However, neither smokers nor active smokers had a greater or lower risk of NMOSD than their nonsmoking counterparts.

4. Discussion

In this study, we found that smoking significantly increased the risk of MS but not of NMOSD, indicating that smoking is not an environmental factor in the etiology of the latter disorder. Three recent studies found that people exposed to passive smoking have a higher risk of MS than those unexposed. We included passive smokers and found similar results.[16–18]

Table 2

Association of smokers (both active and passive) with risk of MS and NMOSD.

Group	n	Smokers	Nonsmokers	P value	OR	95%CI
MS	46	28	18	.027	2.166	1.109 to 4.170
NMOSD	36	18	18	.384	1.392	0.666 to 2.914
NCs	122	51	71			

CI = confidence interval, MS = multiple sclerosis, NCs = normal controls, NMOSD = neuromyelitis optica spectrum disorder, OR = odds ratio.

Table 3

Association of smoking with risk of male MS and NMOSD.

Group	n	Smokers	Nonsmokers	P value	OR	95%CI
MS	12	10	2	.170	3.636	0.736 to 18.000
NMOSD	15	8	7	.763	0.831	0.265 to 2.746
NCs	38	22	16			

CI = confidence interval, MS = multiple sclerosis, NCs = normal controls, NMOSD = neuromyelitis optica spectrum disorder, OR = odds ratio.

Table 4

Association of active smokers with risk of MS and NMOSD.

Group	n	Active smokers	Passive smokers	P value	OR	95%CI
MS	28	12	16	.508	1.375	0.527 to 3.477
NMOSD	18	7	11	.785	1.167	0.409 to 3.473
NCs	51	18	33			

CI = confidence interval, MS = multiple sclerosis, NCs = normal controls, NMOSD = neuromyelitis optica spectrum disorder, OR = odds ratio.

To investigate sex-related differences in exposure to smoking, we further examined whether male or female smokers have an increased risk of MS and NMOSD. Our study demonstrated that male subjects had no increased risk of MS or NMOSD.

To date, the role of smoking in the pathogenesis of NMOSD remains largely unknown. It has been hypothesized that exposure to smoking may alter NMOSD-related CNS autoimmunity, including imbalances in T helper 17/regulatory T cells, aberrant cytokines (IL-6), and antibody secretion.[19] However, the exact role of smoking remains ambiguous and complex, since it exerts dual effects on immunity by either exacerbation of pathogenic immune responses or attenuation of defensive immunity.[8] Interestingly, our study showed higher serum IL-6 levels in smokers with NMOSD than in nonsmokers and NCs (data not shown). This is noteworthy as IL-6 can induce B cells to synthesize antibodies and prompt the differentiation of naïve T cells into T helper 17 cells.[20] More importantly, the anti-IL-6 receptor monoclonal antibody tocilizumab was shown to be highly effective in patients with refractory NMOSD.[21] Nevertheless, more evidence is needed to address this issue.

In conclusion, our preliminary study showed that cigarette smoking may not increase the risk of NMOSD, strongly suggesting that, unlike MS, cigarette smoking might not confer NMOSD susceptibility, at least in the Northern Han Chinese population. However, this study had several limitations. An obvious limitation of this study is its lack of statistical power due to the small number of MS, NMOSD and healthy participants, in addition to smoking individuals in the control group. Therefore, future studies using a larger sample size will help validate the reliability of our results and gain more insight into the role of smoking in NMOSD pathogenesis.

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Author contributions

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