ORIGINAL ARTICLE

Oxidative Stress and Environmental Exposures are Associated with Multiple System Atrophy in Chinese Patients

Linli Zhou, Ying Jiang, Cansheng Zhu, Lili Ma, Qiling Huang, Xiaohong Chen

ABSTRACT: ***Objective***: Oxidative stress is involved in the pathogenesis of multiple system atrophy (MSA). The aim of this study is to examine oxidant biomarkers including homocysteine (Hcys), bilirubin, uric acid, lipids, and potential environmental risk factors and to ascertain whether these data correlate with MSA in a Chinese population. ***Methods***: In this study, serum levels of Hcys, bilirubin, uric acid, and lipids were studied in 55 MSA patients and 76 healthy controls (HCs). Education, anti-parkinsonian agent usage, smoking, drinking, farming, and living area of the subjects also were analyzed. The Unified MSA Rating Scale (UMSARS), Hoehn & Yahr stage, International Cooperative Ataxia Rating Scale, and Mini-Mental State Examination were used to assess the disease severity, the parkinsonism, ataxia, and the cognitive ability of MSA, respectively. ***Results***: The levels of Hcys were higher ($p < 0.001$) and those of total bilirubin ($p = 0.007$), indirect bilirubin ($p = 0.011$), and total cholesterol ($p = 0.046$) were lower in MSA patients than in healthy controls, whereas uric acid levels did not differ significantly between MSA and healthy controls. Moreover, Hcys levels in MSA patients had positive correlations with illness duration ($r_s = 0.422$, $p = 0.001$) and UMSARS-I ($r_s = 0.555$, $p < 0.001$), respectively. High-density lipoprotein cholesterol levels were negatively correlated with UMSARS-I ($r_s = -0.325$, $p = 0.015$). Farming was more frequent in MSA patients (1-20 years: odds ratio, 6.36; $p < 0.001$; >20 years: odds ratio, 10.26; $p = 0.001$), whereas current smoking was less frequent (odds ratio, 0.13, $p = 0.002$). ***Conclusions***: Elevated Hcys and decreased high-density lipoprotein cholesterol may be associated with the disease severity of MSA. Environmental exposures such as farming and smoking may contribute to the occurrence but not the progression of MSA.

RÉSUMÉ: **Le stress oxydatif et l'exposition ambiante associés à l'atrophie multi-systématisée chez des patients chinois.** ***Objectif:*** On le sait, le stress oxydatif est impliqué dans la pathogénèse de l'atrophie multi-systématisée (AMS). Le but de cette étude est donc de passer en revue des marqueurs biologiques, notamment l'homocystéine, la bilirubine, l'acide urique, et des facteurs de risque potentiels d'origine environnementale pour ensuite déterminer dans quelle mesure il existe un lien entre ces données et l'AMS dans un groupe de la population chinoise. ***Méthodes:*** Dans cette étude, nous avons analysé les lipides et les taux sériques d'homocystéine, de bilirubine et d'acide urique de 55 patients atteints d'AMS et de 76 sujets témoins en bonne santé (healthy controls). Nous avons aussi analysé les niveaux d'instruction, la prise de médicaments antiparkinsoniens, le tabagisme, la consommation d'alcool, la pratique de l'agriculture et les lieux de vie de ces individus. À cet effet, nous avons utilisé l'UMSARS-I (Unified MSA Rating Scale), l'échelle de Hoehn et Yahr, l'échelle ICARS (International Cooperative Ataxia Rating Scale) et le test de Folstein (Mini-Mental State Examination) pour évaluer respectivement la gravité de leur maladie, leur syndrome parkinsonien, leur ataxie et leurs capacités cognitives. ***Résultats:*** D'emblée, les niveaux d'homocystéine se sont révélés plus élevés ($p < 0.001$). Les niveaux de bilirubine totale ($p = 0.007$) et de bilirubine indirecte ($p = 0.011$), de même que le taux de cholestérol total ($p = 0.046$), se sont ensuite révélés moins élevés chez les patients atteint d'AMS que chez les sujets témoins en bonne santé alors que les niveaux d'acide urique de ces patients et de ces sujets témoins n'ont pas différé grandement. Qui plus est, nous avons observé une corrélation positive entre les niveaux d'homocystéine des patients atteints d'AMS et, respectivement, la durée de la maladie ($rs = 0.422$, $p = 0.001$) et l'UMSARS-I ($rs = 0.555$, $p < 0.001$). Les taux de lipoprotéines de haute densité ont été aussi négativement corrélés avec l'UMSARS-I ($rs = -0.325$, $p = 0.015$). Fait à noter, la pratique de l'agriculture était plus répandue chez les patients atteints d'AMS (1-20 ans: risque relatif rapproché, 6,36 ; $p < 0.001$; > 20 ans: risque relatif rapproché, 10,26 ; $p = 0.001$), tandis que le tabagisme l'était moins (risque relatif rapproché, 0,13 ; $p = 0.002$). ***Conclusions:*** Il se peut que les niveaux élevés d'homocystéine et que les taux réduits de lipoprotéines de haute densité soient associés à la gravité de l'AMS. Il se peut aussi que des facteurs environnementaux tels que la pratique de l'agriculture et le tabagisme contribuent à l'apparition de l'AMS et non à sa progression.

Keywords: multiple system atrophy, oxidative stress, environmental risk factors, UMSARS-I

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Multiple system atrophy (MSA) is a sporadic neurodegenerative disease involving autonomic dysfunction with parkinsonism or cerebellar ataxia.[1] With the identification of α-synuclein-positive glial cytoplasmic inclusions as a pathological hallmark, MSA was thought as a unique entity within the spectrum of oligodendrogliopathy[2]; however, the etiology of MSA is not clear. Recently, mitochondrial dysfunction and oxidative stress have been considered as risk factors of triggering or exacerbating MSA pathology.[3,4] Some oxidant biomarkers, such as uric acid and lipids, have been considered as potential predictors for the prevalence of MSA.[5,6]

In addition to uric acid and lipids, serum homocysteine (Hcys) and bilirubin are also related with oxidative stress. Hcys plays an important role in some neurodegenerative diseases associated with oxidative stress, such as Alzheimer's disease[7,8] and Parkinson's disease (PD).[8,9] A study also found elevated plasma Hcys levels may predict the outcome of disease severity in PD patients.[10] Inversely, bilirubin contributes to defend against the increased oxidative stress. Some studies have demonstrated low bilirubin levels and oxidative stress occurred in some neuroinflammatory diseases and neurodegenerative diseases.[11-13] Additionally, some environmental factors, especially various occupations, toxin, smoking, drinking, different living area, dietary habits, and use of drugs, were also related to oxidative stress and the progression of MSA.[14-18]

In past decades, Hcys and bilirubin have been explored in numerous neurological diseases; however, these two biomarkers and MSA remain unclear. The aim of this study was to examine serum Hcys, bilirubin, uric acid, lipids, and potential environmental risk factors and to ascertain whether these data correlate with MSA in a Chinese population.

Methods

Clinical Data Collection and Definitions

We retrospectively reviewed the medical records of 55 MSA patients (37 males and 18 females) according to the diagnostic criteria of clinical types, probable MSA and possible MSA[19] from January 2007 to November 2013 admitted to the Third Affiliated Hospital of Sun Yat-sen University in Guangzhou, China. Seventy-six age- and sex-matched healthy subjects (42 males and 34 females) as the healthy controls were consecutively recruited from the Medical Examination Center, the Third Affiliated Hospital of Sun Yat-sen University. The exclusion criteria were listed as: (1) received vitamin supplementation including folic acid, vitamin B12, and vitamin B6 in the past 5 years; (2) having liver or gall diseases; (3) history of neurodegenerative diseases other than MSA; (4) having any other clinically significant medical illnesses; or (5) pregnancy. Data collection was approved by the institution's ethics committee of the Third Affiliated Hospital of Sun Yat-sen University. All people in this study have given their informed consent before inclusion.

Data of age, sex, education level, anti-parkinsonian agent usage, and illness duration as well as the exposure factors, including smoking habits, drinking habits, farming history, and rural living history, were collected. The disease severity of MSA patients was assessed by The Unified MSA Rating Scale I (UMSARS-I). Every one of the 12 items including speech, swallowing, handwriting, cutting food and handling utensils, dressing, hygiene, walking, falling, orthostatic symptoms, urinary function, sexual function and bowel function possessed 4 points in UMSARS-I scoring, making the max scores as 48.[20] The Hoehn & Yahr (H&Y) stage and International Cooperative Ataxia Rating Scale (ICARS) were used to evaluate the parkinsonism and ataxia of the patients respectively. The cognitive condition of each subject was determined by Mini-Mental State Examination (MMSE).

Serum Hcys, Bilirubin, Uric Acid, and Lipids Determination

The concentrations of serum Hcys (normal range, 3.7-13.9 μmol/L), total bilirubin (Tbil) (normal range, 4.0-23.9 μmol/L), indirect bilirubin (Ibil) (normal range, 2.56-20.9 μmol/L), uric acid (normal range, 90-420 μmol/L), and lipid including total cholesterol (TC) (normal range, 3.10-5.70 mmol/L), triglyceride (normal range, 0.34-1.92 mmol/L), high-density lipoprotein cholesterol (HDL-C) (normal range, 0.78-2.00 mmol/L), and low-density lipoprotein cholesterol (LDL-C) (normal range, 2.07-3.10 mmol/L) were determined in our hospital. Blood samples were obtained at rest and after a 12-hour fasting period.

Statistical Analysis

All statistical analyses were performed by the Statistical Program for Social Sciences (SPSS) statistical software (version 13.0, Chicago, IL, USA). All the data of continuous variables, including age, illness duration, UMSARS-I, H&Y, ICARS, MMSE, Hcys, Tbil, Ibil, uric acid, TC, triglyceride, HDL-C, and LDL-C were presented as mean ± standard deviation and the categorical data such as sex, education level, dopaminergic medication usage, smoking habits, drinking habits, farming history, and rural living history were shown as percentages. Statistical significance was set at $p < 0.05$. Student's t-test or one-way analysis of variance was performed to determine the differences in continuous data between MSA patients and the controls, and chi-square test was performed for categorical variables. A Spearman's correlation coefficient was used to determine the associations between Hcys, bilirubin, uric acid, lipids, and the clinical variables, including illness duration, UMSARS-I, H&Y, ICARS, and MMSE. Logistic regression was used to analyze exposure data (smoking habits, drinking frequency, farming history, and rural living history) and to determine odds ratios (OR) and 95% confidence intervals (OR [95% CI]).

Results

Patient Characteristics

Fifty-five MSA patients including 39 probable MSA and 16 possible MSA (37 males [67.3%] and 18 females (32.7%]) and 76 healthy control subjects (42 males [55.3%] and 34 females [44.7%]) were enrolled in this study (Table 1). The MSA subjects were categorized as MSA-P (23 [41.8%]) and MSA-control (32 [58.2%]), and 20 MSA patients (36.4%) received anti-parkinsonian agents (Table 1). As shown in Tables 1 and 2, there were no significant differences in mean ages, sex distribution, and education levels between MSA patients and controls. Exposure factors before the onset of the disease in the MSA group and the index age in the control group are listed in Table 4; the exposures at the admission time are shown in Table 5.

The mean illness duration of MSA patients was 2.62 ± 2.20 years; the mean UMSARS-I scores were 10.92 ± 4.40. The H&Y stage of MSA patients was significantly higher than that of the

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Table 1: Sex distribution, education level, clinical type, and anti-parkinsonian agent usage of MSA patients and controls

		MSA patients, N (%)	Controls, N (%)	χ^2	p
Sex	Male	37 (67.3)	42 (55.3)	1.923	0.166
	Female	18 (32.7)	34 (44.7)		
Education level	<12 years	39 (70.9)	45 (59.2)	1.898	0.168
	>12 years	16 (29.1)	31 (40.8)		
Clinical type	MSA-P	23 (41.8)	—	—	—
	MSA-C	32 (58.2)			
Using anti-parkinsonian agents	Yes	20 (36.4)	—	—	—
	No	35 (63.6)			

All 20 MSA patients treated with anti-parkinsonian agents adopted the treatment of levodopa (0.375-1.000 g/day); four patients received a combination with dopamine agonists (two with pramipexole [0.375 and 0.75 mg/day], two with piribedil [50 and 100 mg/day]), two patients received a combination with amantadine (100 mg/day), and one patient received a combination of anticholinergic agents (4 mg/day).

controls (1.53 ± 1.42 vs 0.36 ± 0.64, $p < 0.001$). The MMSE mean scores of MSA patients were significantly lower than those of controls (24.70 ± 5.45 vs 28.14 ± 2.00, $p < 0.001$) (Table 2).

Comparison of Serum Hcys, Bilirubin, Uric Acid, and Lipid Levels Between MSA Patients and Controls

Serum Hcys levels in MSA patients were higher than those in the controls (13.52 ± 4.56 vs 10.28 ± 3.31 μmol/L, $p < 0.001$) (Table 2). Serum levels of bilirubin including Tbil and Ibil were lower in MSA patients than those in controls (11.61 ± 4.21 vs 13.88 ± 5.30 μmol/L, $p = 0.007$; 8.28 ± 3.05 vs 9.86 ± 3.98 μmol/L, $p = 0.011$, respectively). There were no significant differences in the uric acid levels between MSA patients and controls. In the lipids data, only TC levels in MSA were significantly lower than those in controls (4.45 ± 1.22 vs 4.99 ± 1.69 mmol/L, $p = 0.046$).

Table 2: Age, Hcys, bilirubin, uric acid, lipid, illness duration, UMSARS-I, H&Y, ICARS, and MMSE in MSA and controls

	MSA patients	Controls	*t*	p
Age (years)	59.33 ± 10.47	60.41 ± 11.50	0.551	0.583
Hcys (μmol/L)	13.52 ± 4.56	10.28 ± 3.31	4.473	<0.001
Tbil (μmol/L)	11.61 ± 4.21	13.88 ± 5.30	2.726	0.007
Ibil (μmol/L)	8.28 ± 3.05	9.86 ± 3.98	2.565	0.011
Uric acid (μmol/L)	316.02 ± 109.21	302.49 ± 105.47	0.714	0.477
TC (mmol/L)	4.45 ± 1.22	4.99 ± 1.69	2.011	0.046
TG (mmol/L)	1.59 ± 1.86	1.64 ± 2.47	0.127	0.899
HDL-C (mmol/L)	1.17 ± 0.33	1.22 ± 0.36	0.858	0.393
LDL-C (mmol/L)	3.03 ± 2.20	3.16 ± 1.02	0.437	0.663
Illness duration (years)	2.62 ± 2.20	—	—	—
UMSARS-I	10.92 ± 4.40	0.92 ± 1.30	16.367	<0.001
H&Y	1.53 ± 1.42	0.36 ± 0.64	5.717	<0.001
ICARS	30.18 ± 17.08	1.75 ± 3.37	12.172	<0.001
MMSE	24.70 ± 5.45	28.14 ± 2.00	4.524	<0.001

Associations Between Serum Hcys, Bilirubin, Uric Acid, Lipids, and Disease Severity of MSA

Significant correlations between Hcys and illness duration/UMSARS-I ($r_s = 0.422$, $p = 0.001$; $r_s = 0.555$, $p < 0.001$, respectively) occurred in MSA patients. And HDL-C levels had a negative correlation with UMSARS-I ($r_s = -0.325$, $p = 0.015$) and a positive correlation with H&Y ($r_s = 0.398$, $p = 0.003$). LDL-C levels also had positive correlations with ICARS ($r_s = 0.281$, $p = 0.037$) and MMSE ($r_s = 0.303$, $p = 0.024$). There were no associations between serum bilirubin/uric acid and disease severity of MSA (Table 3 and Fig. 1).

Exposed Factors in MSA Patients

Current smoking was less frequent in MSA patients than in controls (adjusted OR, 0.13; 95% CI, 0.03-0.48; $p = 0.002$). And farming was more frequent in MSA patients than in controls (1-20 years: adjusted OR, 6.36; 95% CI, 2.36-17.12; $p < 0.001$; >20 years: adjusted OR, 10.26; 95% CI, 2.68-39.30; $p = 0.001$). A significant difference between MSA patients and controls occurred in the rural living analysis (crude OR, 2.91; 95% CI, 1.35-6.27; $p = 0.006$), but that disappeared after adjustment for other factors (Table 4). There were no significant associations between UMSARS-I and these exposed factors including smoking, drinking, duration of farming, and rural living history at the admission time (Table 5).

Discussion

More and more clinical data and experimental studies have considered whether oxidative stress would play an important role in the pathogenesis of MSA.[3-6] Oxidative stress can induce neuronal damage, modulate intracellular signaling, and ultimately lead to neuronal death by apoptosis or necrosis.[21] Our research showed that Hcys levels in MSA were significantly higher than those in the controls, whereas serum levels of Tbil and Ibil were lower in MSA patients. Hcys is a risk factor for neurotoxicity and leads to brain damage in humans.[22] Elevated Hcys levels are widely reported to be associated with neurodegenerative diseases through oxidative stress.[21,23,24] Bilirubin, the end-product of heme metabolism, has a stronger antioxidant capacity than many other antioxidants, including α-tocopherol, superoxide dismutase,

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Table 3: Correlation between Hcys, bilirubin, uric acid, lipids, and clinical variables, including illness duration, UMSARS-I, H&Y, ICARS, and MMSE in MSA patients

	Hcys		TBIL		IBIL		Uric acid	
Clinical variables	r_s	p	r_s	p	r_s	p	r_s	p
Illness duration	0.422	0.001	0.215	0.116	0.224	0.101	−0.036	0.796
UMSARS-I	0.555	<0.001	0.163	0.234	0.147	0.285	0.197	0.149
H&Y	0.198	0.147	−0.037	0.787	0.038	0.784	−0.219	0.109
ICARS	−0.146	0.286	−0.028	0.832	−0.007	0.960	0.143	0.299
MMSE	−0.126	0.360	−0.002	0.986	−0.084	0.540	0.255	0.060
	TC		**TG**		**HDL-C**		**LDL-C**	
Clinical variables	r_s	p	r_s	p	r_s	p	r_s	p
Illness duration	−0.083	0.545	0.036	0.795	0.001	0.992	−0.170	0.215
UMSARS-I	−0.163	0.235	0.126	0.358	−0.325	0.015	−0.085	0.535
H&Y	0.063	0.646	−0.193	0.159	0.398	0.003	0.047	0.732
ICARS	0.187	0.172	0.161	0.239	−0.095	0.488	0.281	0.037
MMSE	0.165	0.229	0.118	0.390	−0.036	0.791	0.303	0.024

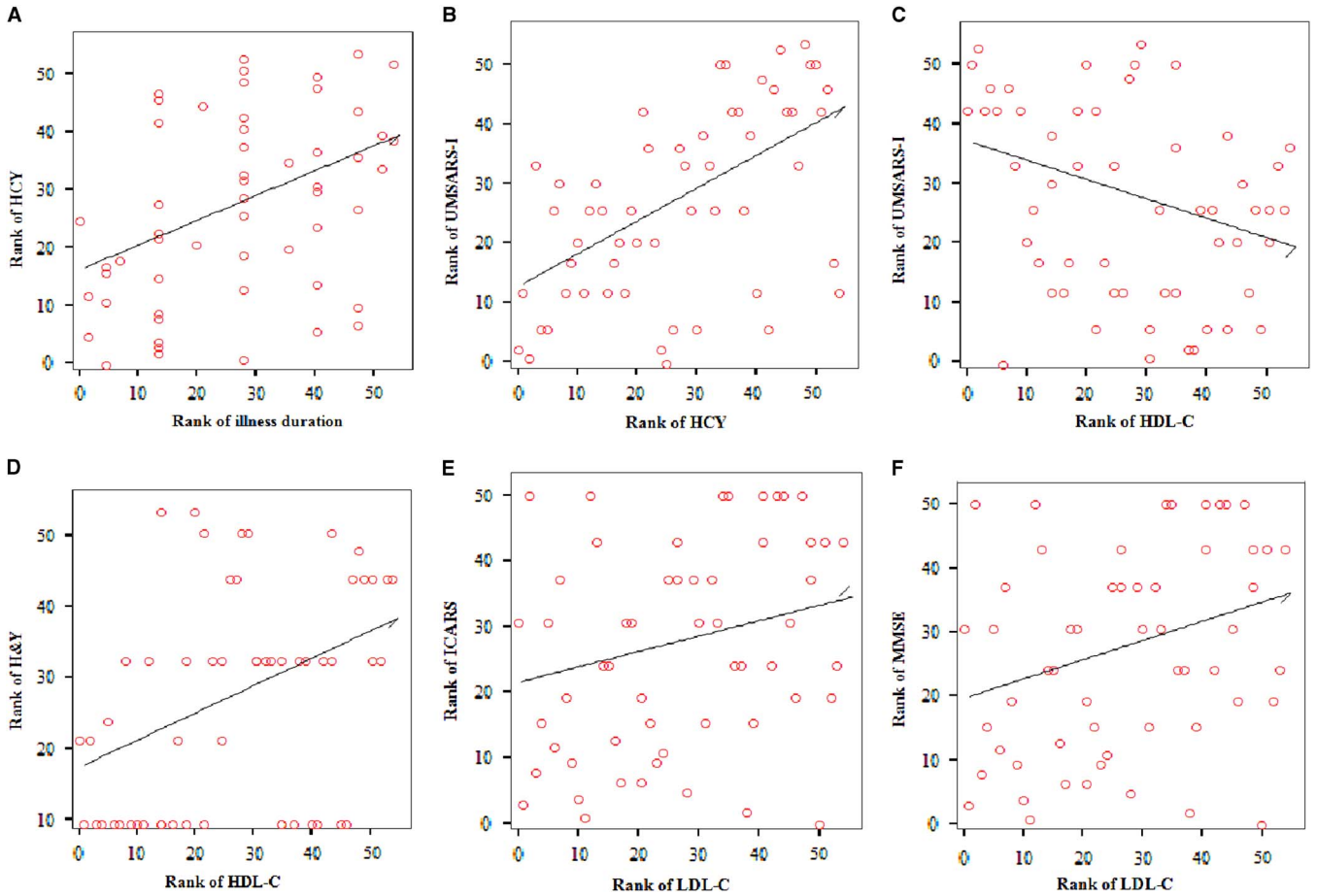

Figure 1: *Correlation between the serum oxidative biomarkers and illness duration, UMSARS-I, H&Y, ICARS, and MMSE in MSA patients. (A) Hcys levels have a positive association with illness duration. (B) Hcys levels are positively associated with UMSARS-I. (C) Serum HDL-C has a negative correlation with UMSARS-I. (D) Serum HDL-C negatively correlates with H&Y stage. (E) Serum LDL-C positively correlates with ICARS scores. (F) Serum LDL-C positively correlates with MMSE scores.*

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Table 4: Smoking, drinking, and farming and rural living exposures (at the onset of MSA) of MSA patients and controls

Exposed factors	MSA	Controls	Crude OR (95% CI)	p	Adjusted OR (95% CI)[a]	p
Smoking history, N (%)						
Never	50 (90.9)	54 (71.1)	1 (Ref.)	—	1 (Ref.)	—
Former	1 (1.8)	5 (6.6)	0.22 (0.02-1.91)	0.169	0.12 (0.01-1.33)[a]	0.085
Current	4 (7.3)	17 (22.4)	0.25 (0.08-0.81)	0.020	0.13 (0.03-0.48)[a]	0.002
Drinking						
Never	51 (92.7)	65 (85.5)	1 (Ref.)	—	1 (Ref.)	—
Ever	4 (7.3)	11 (14.5)	0.46 (0.14-1.54)	0.210	1.38 (0.23-8.13)[b]	0.725
Farming history						
Never	16 (29.1)	47 (61.8)	1 (Ref.)	—	1 (Ref.)	—
1-20 years	28 (50.9)	23 (30.3)	3.58 (1.62-7.89)	0.002	6.36 (2.36-17.12)[c]	<0.001
>20 years	11 (20.0)	6 (7.9)	5.39 (1.71-16.93)	0.004	10.26 (2.68-39.30)[c]	0.001
Rural living						
Never	13 (23.6)	36 (47.6)	1 (Ref.)	—	1 (Ref.)	—
Ever	42 (76.4)	40 (52.6)	2.91 (1.35-6.27)	0.006	0.85 (0.18-3.97)[d]	0.837

Without statistical analysis results. Adjusted OR indicates odds ratios adjusted for sex, age and education level;
[a]Adjusted for drinking, farming, and rural living.
[b]Adjusted for smoking, farming, and rural living.
[c]Adjusted for smoking, drinking, and rural living.
[d]Adjusted for drinking, smoking and farming.

and catalase.[25] Moreover, higher serum Hcys levels are associated with longer illness duration and higher UMSARS-I scores, and probably suggests that higher levels of Hcys may predict worse disease severity in MSA. However, the correlation between Hcys and illness duration/UMSARS-I is weak, which may be attributed to small sample size and other unknown factors affecting Hcys and the disease severity of MSA. Although MMSE scores of MSA patients were lower than controls, and dementia has been widely reported to correlate with higher Hcys levels,[7,26] the correlation between Hcys and MMSE in MSA patients was not shown in this study. This result suggests that Hcys is not the main factor affecting cognitive impairment in MSA, although oxidative stress exists in both dementia and MSA. Uric acid is also considered an antioxidant and has been found to play a key role in the risk and progression of some neurodegenerative diseases associated with oxidative stress, such as PD,[27] amyotrophic lateral sclerosis,[28] and MSA.[5] However, we did not find any significant changes in the uric acid levels in patients with MSA in this study.

Table 5: Association between different exposure factors (at admission time) and UMSARS-I in MSA patients

Exposure factors		N (%)	UMSARS-I	*F/t*	p
Smoking habits	Never	49 (89.1)	10.86 ± 4.54	0.059	0.942
	Former	3 (5.4)	11.67 ± 2.89		
	Current	3 (5.4)	11.33 ± 4.16		
Drinking habits	Never	51 (92.7)	10.96 ± 4.45	0.200	0.842
	Ever	4 (7.3)	10.50 ± 4.20		
Farming history	Never	16 (29.1)	11.13 ± 3.76	1.261	0.292
	1-20 years	27 (49.1)	10.11 ± 4.29		
	>20 years	12 (21.8)	12.50 ± 5.27		
Rural living	Never	13 (23.6)	11.15 ± 3.93	0.211	0.834
	Ever	42 (76.4)	10.86 ±4.57		

F = statistics for smoking habits and farming history; *t* = statistics for drinking habits and rural living.

In this study, the results suggest that the serum TC is significantly decreased in MSA patients. HDL-C still plays a protective role in the severity of MSA because its negative correlation with UMSARS-I scores. Increased LDL-C exerts a beneficial role in ataxia and cognition according to its positive correlations with ICARS and MMSE in MSA patients. These results were similar to the study of another group[6] that suggested that lower cholesterol such as TC, HDL-C, and LDL-C might increase the risk of MSA. Lower TC and HDL-C were demonstrated to increase the risk of MSA.[29] Cholesterol in the brain membranes may modulate the conformational state of α-synuclein or even directly as a major component of α-synuclein.[30] Lower cholesterol levels may lead to the abnormity of α-synuclein and contribute to the pathogenesis of MSA. Another interesting finding is that higher HDL-C has a positive correlation with H&Y stage, although it has a negative correlation with UMSARS-I scores. This is consistent with the finding of Cao et al that serum HDL-C was increased in MSA-P patients.[6] Additionally, HDL-C was recently reported to have positive association with the duration of PD.[31] A possible explanation is that progressive motor impairment such as exercise may affect the HDL-C metabolism.[32] Improved movements of PD patients were associated with a reduction in HDL-C.[33]

Epidemiological studies have shown that oxidative stress played key functions in the pathogenesis of MSA. For example, farming involves a heterogeneous exposure to different chemical

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and biological factors (pesticides, solvents, mycotoxins, dust, fuels, oils, fertilizers, farm animals),[34] which might interfere with the mitochondrial electron transport chain and induce oxidative stress to trigger or exacerbate MSA.[14,18] In this study, we also found that those involved in farming show an increased risk of MSA. And we found that current smoking appears to be less frequent among MSA patients than controls, which is similar to the European study in MSA[35] and the Spanish study in PD,[36] but opposite to the Korean epidemiological study.[18] In terms of protective effects, nicotine was reported as an antioxidant, which may be intracellular through the activation of the nicotinic receptors or extracellular by acting as a radical scavenger.[37] Additionally, nicotine can also act as an agonist of neuronal nicotinic receptors, which modulates functions relevant to PD via stimulation of dopaminergic transmission in the nigrostriatal pathway.[38] We also found that exposures did not have significant associations with UMSARS-I in MSA patients, suggesting that the environmental exposures probably did not worsen or ameliorate the disease severity, but only influenced the occurrence of MSA. In addition to these factors included, other environmental exposure factors were found to be related to MSA in other studies, such as being a machine operator and assembler and using herbal medications associated with increased risk for MSA, whereas consumption of meat, seafood, tea, and coffee and the use of antihypertensive medication, aspirin, and vitamins was associated with a decreased risk.[17,18] These epidemiological data prompted the belief that some environmental factors may provide clues to the etiopathogenesis of MSA.

In summary, this study found that elevated Hcys and decreased HDL-C levels may be associated with the disease severity of MSA. Environmental exposures such as farming and smoking may contribute to the occurrence of MSA, but not the progression. The results suggest that oxidative stress is involved in the pathogenesis of MSA; however, further studies are still needed for better understanding the etiology of this disease.

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LZ and YJ contributed equally to this work.

Disclosures

The authors declare there are no conflicts of interest.

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