J Neurol (2013) 260:2511–2515
DOI 10.1007/s00415-013-7006-z

ORIGINAL COMMUNICATION

Uric acid is associated with the prevalence but not disease progression of multiple system atrophy in Chinese population

Bei Cao · XiaoYan Guo · Ke Chen · Wei Song · Rui Huang · Qian-Qian Wei · Bi Zhao · Hui-Fang Shang

Received: 30 March 2013 / Revised: 10 June 2013 / Accepted: 10 June 2013 / Published online: 26 June 2013

Abstract Oxidative stress is involved in the pathogenesis of multiple system atrophy (MSA). Uric acid has an antioxidative effect. Our aim is to clarify the correlations between serum uric acid and MSA in Chinese population. A total of 234 patients with probable MSA and 240 age- and gender- matched healthy controls were included in the study. The serum uric acid levels of all the patients and controls were evaluated. The Unified MSA Rating Scale (UMSARS) was used to assess the severity and the mean rate of annualized changes of UMSARS to assess the progression of MSA. The mean age of MSA patients was 58.90 ± 9.00 years and the mean disease duration was 2.60 ± 1.75 years. The serum uric acid levels of MSA patients were significantly lower than that of controls in males ($p = 0.0001$). The occurrence of MSA was increased in the lowest uric acid quartiles compared with the highest uric acid quartiles ($p = 0.005$). In a gender-specific analysis, increased occurrence was found in the lowest quartiles and second quartiles compared with the highest quartiles in males ($p = 0.001$ and $p = 0.0001$ respectively), but not in females. No correlation was found between the mean rate of annualized changes and serum levels of uric acid, as well as other independent factors, such as age, BMI, gender, subtype (C-type or P-type) and disease duration at the initial visit in 107 followed-up patients. MSA patients have lower levels of serum uric acid than controls. High levels of serum uric acid may be associated with a lower prevalence of MSA in the Chinese population, especially in males. However, serum uric acid does not deteriorate or ameliorate the progression of MSA.

Keywords Multiple system atrophy · Uric acid · Prevalence · Disease progression

B. Cao · X. Guo · K. Chen · W. Song · R. Huang · Q.-Q. Wei · B. Zhao · H.-F. Shang (✉)
Department of Neurology, West China Hospital, SiChuan University, Chengdu 610041, Sichuan, China
e-mail: hfshang@yahoo.com

Introduction

Multiple system atrophy (MSA) is a sporadic and adult-onset neurodegenerative disease characterized by parkinsonism, cerebellar ataxia, autonomic dysfunction and pyramidal dysfunction in any combination [1]. The main neuropathological features of MSA are abnormal α-synuclein positive cytoplasmic inclusions presented in oligodendrocytes, neuronal loss, gliosis, myelin pallor and axonal degeneration in striatonigral and/or olivopontocerebellar systems [1]. The etiology of MSA is not yet fully understood. Recently, some epidemiological studies found that occupational exposure to some chemicals that interfere with the mitochondrial electron transport chain and increase oxidative stress may increase the risk of MSA [2, 3]. An animal study found that a compound 3-nitropropionic acid (3-NP) with a function of inhibition mitochondrial complex II could induce MSA in an animal model [4–6]. These findings suggest that oxidative stress is involved in the pathogenesis of MSA [2, 4, 6–9].

Uric acid, a natural antioxidant, has been found to play a key role in the risk and progression of some neurodegenerative diseases with the pathogenesis of oxidative stress [10–13]. For example, many clinical studies have found that high levels of serum uric acid decreased the risk of Parkinson's disease (PD) [14–16] and amyotrophic lateral sclerosis (ALS) [17, 18]. Furthermore, some studies showed that high levels of serum uric acid decreased the

progression of PD [19] and ALS [17]. However, other studies found that high levels of serum uric acid decreased the risk [20, 21] and progression [22–24] of PD and ALS in male subjects, but not in females.

At present, the associations between serum uric acid and MSA remain largely unknown. There were two studies from Korea focused on the association of uric acid and the progression of MSA. However, the results were not consistent with each other. Lee JE et al. [25] studied 52 MSA patients, most of whom had MSA type C (48 patients), and found that high uric acid slowed down the progression of MSA. Another large sample Korean study including 455 MSA patients found that uric acid was not associated with survival of MSA [26]. However, the study did not consider the influence of metabolism factors, such as BMI, hypertension and diabetic mellitus, which could have an impact on the level of uric acid levels. To further verify the relationship between serum uric acid and MSA, we conducted this prospective study in a Chinese population.

Patients and methods

A total of 234 Chinese MSA patients admitted in the Department of Neurology, West China Hospital, Sichuan University from November 2006 to May 2013 were enrolled in the study. All the MSA patients met the probable MSA clinical diagnostic criteria [1]. The control group was composed of 240 age- and gender-matched subjects from the Medical Examination Center (MEC), West China Hospital of Sichuan University. None of the controls had any neurological diseases. The fasting serum uric acid concentrations of the MSA patients and controls were measured in the clinical laboratory of the West China Hospital of Sichuan University. Clinical information, including gender, age, BMI, histories of hypertension and diabetes mellitus, were collected. The severity of MSA was assessed by the Unified MSA Rating Scale (UMSARS), which had been thought to have a high criteria-related validity [27, 28]. The progression of MSA was assessed by the annualized rate of changes in the UMSARS scores, which was calculated by the following formula: [(total UMSARS score at the last visit − total UMSARS score at the baseline visit)/number of days between the assessments] × 365 day [25]. The study was approved by the Sichuan University Ethics Committee.

Data analyses

All continuous data including mean age, disease duration, BMI and serum uric acid level were presented as mean ± standard deviation and all categorical variables including gender, subtype (C-type or P-type), histories of hypertension and diabetes mellitus were presented as percentages. The differences in continuous data and categorical variables between MSA patients and controls were studied by student's t test and Chi-square test respectively. The levels of serum uric acid were assigned into quartiles based on its distribution in the controls and the highest quartile was set as a reference for analysis. Odds ratios (ORs) and 95 % confidence intervals (CIs) were measured by Chi-square tests. We employed the mean rate of annualized changes of the UMSARS score as a dependent variable, and the uric acid level, age, disease duration at initial visit, gender, BMI and subtype of MSA as independent factors. All the statistical analyses were performed using commercially available software (SPSS, version 19.0), and a $p < 0.05$ was deemed statistically significant.

Results

The demographic characteristics and serum uric acid levels of included MSA patients and controls are listed in Table 1. The mean disease duration of MSA patients was 2.60 ± 1.75 years. There were no significant differences in mean age, gender distribution, BMI and histories of hypertension and diabetes mellitus between MSA patients and controls (Table 1). Except for disease duration at initial visit and the mean interval between baseline and last assessment, the rest of the continuous data in our study were normally distributed by the Kolmogorov–Smirnov test. Serum uric acid levels were lower in all MSA patients than that in controls (5.01 ± 1.36 vs. 5.31 ± 1.33, $p = 0.01$, Table 1). However, in a gender-specific analysis, this difference was only found in male patients compared with controls (5.50 ± 1.30 vs. 6.15 ± 1.19, $p = 0.0001$, Table 1).

The ORs of MSA patients according to the uric acid profile quartiles of the controls are listed in Table 2. The univariant analysis of uric acid profiles found that subjects with the lowest uric acid quartiles had higher occurrences of MSA compared with those with the highest uric acid quartiles (OR = 2.10, CI = 1.24–3.56, $p = 0.005$, Table 2). In a gender-specific analysis, a significant higher occurrence of MSA was found in the second and lowest quartiles compared with those with the highest quartiles in males (OR = 3.63, CI = 1.77–7.46, $p = 0.0001$; OR = 4.67, CI = 1.84–11.85, $p = 0.001$, respectively, Table 2). However, the serum uric acid levels were not associated with either increased or decreased occurrence of MSA in females (Table 2).

A total of 133 patients were followed-up; however 26 of these patients have since died. The longitudinal data of 107 patients were analyzed for the progression of MSA. Among 107 MSA patients, including 56 males and 51 females, 67 had MSA-C and 30 had MSA-P. All patients were assessed

Table 1 Demographic characteristics and serum uric acid levels of patients with MSA and control subjects

	MSA patients ($n = 234$)			Controls ($n = 240$)			*p-value*		
	All subjects	Men ($n = 121$)	Women ($n = 113$)	All subjects	Men ($n = 120$)	Women ($n = 120$)	p_{ALL}	p_M	p_W
Age (year)	58.90 ± 9.00	58.98 ± 9.50	58.81 ± 8.49	58.75 ± 8.23	58.80 ± 8.01	58.70 ± 8.48	0.85	0.877	0.92
Hypertension (%)	26 (11)	15 (12)	11 (9)	24 (10)	14 (12)	10 (8)	0.89	1.0	0.82
Diabetes mellitus (%)	21 (9)	12 (10)	9 (8)	20 (8)	13 (11)	7 (6)	0.87	0.84	0.61
Uric acid (mg/l)	5.01 ± 1.36	5.50 ± 1.30	4.48 ± 1.12	5.31 ± 1.33	6.15 ± 1.19	4.51 ± 0.92	0.01	0.0001	0.81
BMI	23.06 ± 2.77	23.49 ± 2.53	22.61 ± 2.94	23.60 ± 3.11	24.12 ± 3.15	23.08 ± 2.99	0.06	0.11	0.26
MSA-P/MSA-C	100/134	43/78	57/56						
Disease duration (year)	2.60 ± 1.75	2.71 ± 1.81	2.48 ± 1.68						

MSA multiple system atrophy, p_{ALL} all subjects comparison between MSA patients and controls, p_M men, comparison between MSA patients and controls, p_W women, comparison between MSA patients and controls

Table 2 Odds ratios (OR) of patients with MSA based on uric acid profile quartiles

Uric acid (mg/dl)	All subjects			Men			Women		
	Case/control (234/240)	Adjusted ORs (95 % CI)	*p*-value	Case/control (121/120)	Adjusted ORs (95 % CI)	*p*-value	Case/control (113/120)	Adjusted ORs (95 % CI)	*p*-value
<4.35	80/60	2.10 (1.24–3.56)	0.005	20/8	4.67 (1.84–11.85)	0.001	60/52	0.58 (0.16–3.85)	0.39
4.35–5.28	59/60	1.56 (0.90–2.67)	0.111	35/18	3.63 (1.77–7.46)	0.0001	24/42	0.29 (0.078–1.049)	0.100
5.28–6.15	57/60	1.50 (0.87–2.59)	0.144	36/38	1.77 (0.94–3.34)	0.078	21/22	0.274 (0.13–1.82)	0.48
>6.15	38/60	1		30/56	1		8/4	1	

MSA multiple system atrophy

by the UMSARS at initial visit and at the last visit. The mean age of these followed-up MSA patients was 58.83 ± 8.88 years and the mean duration at the initial visit was 4.34 ± 1.84 years. The mean level of serum uric acid was 5.02 ± 1.37 mg/dl and mean BMI was 23.29 ± 2.70. The mean interval between baseline and last assessment of UMSARS-1 was 1.05 ± 0.70 years, and the mean rate of annualized changes in the UMSARS score was 18.08 ± 10.40. Through multiple regression analysis, we found that the level of uric acid, age, disease duration at the initial visit, BMI, gender, and subtype of MSA did not significantly correlate with the mean rate of annualized changes in the UMSARS.

Discussion

To our knowledge, this is the first study exploring the association of serum uric acid levels and the prevalence of MSA. Our research found that serum uric acid was significantly lower than that of healthy controls. High levels of serum uric acid may be associated with a low prevalence of MSA in the Chinese population, especially in males. Uric acid levels neither worsened nor ameliorated the progression of MSA.

Significantly low levels of uric acid observed in our Chinese MSA patients compared to that in controls was consistent with our findings that low levels of serum uric acid increases the occurrence of MSA, and is similar to the results of previous studies on other neurodegenerative diseases such as PD [14, 15, 19, 21] and ALS [17]. Accumulated epidemiological data and animal-based evidence have highlighted the notion that oxidative stress plays a key role in the pathogenesis of MSA [2, 4, 6–9]. For example, some epidemiological studies [2, 7] found that occupational exposure to pesticides, insecticides, or chemicals which interfere with the mitochondrial electron transport chain and induce oxidative stress may increase the risk of MSA. 3-NP as an environment toxin, which can inhibit mitochondrial complex II and enhance oxidative modification of α-synuclein, has been reported to induce MSA in an animal model [4–6]. In vitro experiments have been revealed that uric acid is a scavenger of peroxyl radicals (RO_2), hydroxyl radicals (OH) and singlet oxygen

[10]. Uric acid has been reported to inhibit the radicals generated by the decomposition of peroxynitrite, a strong oxidizing agent which is able to interact with almost all important cell constituents inducing cell injuries [29]. Besides its action as a radical scavenger, uric acid can also chelate metal ions such as iron and copper, and convert them to poorly reactive forms, which are unable to catalyze free-radical reactions [30–32]. Although the exact mechanism of low uric acid levels increasing the occurrence of MSA remains unclear, the antioxidative function of uric acid may contribute to such an association.

Our finding of the lower serum uric acid levels increasing the occurrence of MSA only in males may be due to the significantly higher uric acid levels in males than in females. Further, we speculate that a biological interaction between gender specific hormones and uric acid might play a key role in the strong association between uric acid level and the occurrence of MSA in men.

Our study found that the level of uric acid did not worsen or ameliorate the progression of MSA. Our finding was supported by the Korean study [26], although some metabolism factors such as BMI, hypertension and diabetic mellitus, which could have an impact on uric acid levels, were not taken into consideration in that study. In the current study, we excluded the effect of BMI, hypertension and diabetic mellitus on uric acid. Our finding was not consistent with the positive finding of another small sample Korean study [25]. The sample selection bias may contribute to such a difference since most of the included patients in that study were patients with MSA subtype C. Whether uric acid has an important effect on the occurrence but not the progression of MSA remains largely unknown. With our findings, we understand that uric acid may have an important function in the pathogenesis but not in the progression of MSA. Considering the complications of high uric acid in aging individuals, appropriate medicines should be provided to treat high serum uric acid level in patients with MSA.

Some limitations of our study should be considered. First, part of our study involved a case-control design, and the results did not reflect the longitudinal effects of uric acid. The control subjects were from the Medical Examination Center, and they may contribute to the occurrence of bias because these subjects were from the urban population and may have had a better economic situation. Additionally, we have to consider the selection bias of patients in our follow-up study. The disease severity was variable among our patients, and patients with less severe symptoms had a higher rate of return visits while patients with severe symptoms had a lower rate of return visit. Moreover, other factors that may influence the risk of MSA, such as smoking, were not adjusted in the statistical analysis [33, 34]. Although our study is a prospective study, the small sample size and the short follow-up period limited the significance of our finding. Future studies with a larger sample size and longer follow-up period should be considered.

Conclusion

MSA patients have lower levels of serum uric acid than healthy controls. Our study found that low levels of uric acid may be associated with the prevalence of MSA in the Chinese population, especially in males. However, uric acid did not contribute to the progression of MSA. Further prospective studies with larger sample sizes should be conducted to confirm such a relationship.

Acknowledgments We thank the patients and their families for their participation in this project. This study was supported by funding from the West China Hospital of Sichuan University.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Wenning GK, Colosimo C, Geser F, Poewe W (2004) Multiple system atrophy. Lancet Neurol 3:93–103
2. Nee LE, Gomez MR, Dambrosia J, Bale S, Eldridge R, Polinsky RJ (1991) Environmental-occupational risk factors and familial associations in multiple system atrophy: a preliminary investigation. Clin Auton Res 1:9–13
3. Vanacore N (2005) Epidemiological evidence on multiple system atrophy. J Neural Transm 112:1605–1612
4. Fernagut PO, Tison F (2012) Animal models of multiple system atrophy. Neurosci 211:77–82
5. Ubhi K, Lee PH, Adame A, Inglis C, Mante M, Rockenstein E, Stefanova N, Wenning GK, Masliah E (2009) Mitochondrial inhibitor 3-nitroproprionic acid enhances oxidative modification of alpha-synuclein in a transgenic mouse model of multiple system atrophy. J Neurosci Res 87:2728–2739
6. Stefanova N, Tison F, Reindl M, Poewe W, Wenning GK (2005) Animal models of multiple system atrophy. Trends Neurosci 28:501–506
7. Vanacore N, Bonifati V, Fabbrini G, Colosimo C, De Michele G, Marconi R, Stocchi F, Nicholl D, Bonuccelli U, De Mari M, Vieregge P, Meco G (2005) Case-control study of multiple system atrophy. Mov Disord 20:158–163
8. Ubhi K, Low P, Masliah E (2011) Multiple system atrophy: a clinical and neuropathological perspective. Trends Neurosci 34:581–590
9. Stefanova N, Georgievska B, Eriksson H, Poewe W, Wenning GK (2012) Myeloperoxidase inhibition ameliorates multiple system atrophy-like degeneration in a transgenic mouse model. Neurotox Res 21:393–404
10. Ames BN, Cathcart R, Schwiers E, Hochstein P (1981) Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA 78:6858–6862

11. Glantzounis GK, Tsimoyiannis EC, Kappas AM, Galaris DA (2005) Uric acid and oxidative stress. Curr Pharm Des 11:4145–4151
12. Scott GS, Cuzzocrea S, Genovese T, Koprowski H, Hooper DC (2005) Uric acid protects against secondary damage after spinal cord injury. Proc Natl Acad Sci USA 102:3483–3488
13. Amaro S, Planas AM, Chamorro A (2008) Uric acid administration in patients with acute stroke: a novel approach to neuroprotection. Expert Rev Neurother 8:259–270
14. Winquist A, Steenland K, Shankar A (2010) Higher serum uric acid associated with decreased Parkinson's disease prevalence in a large community-based survey. Mov Disord 25:932–936
15. Davis JW, Grandinetti A, Waslien CI, Ross GW, White LR, Morens DM (1996) Observations on serum uric acid levels and the risk of idiopathic Parkinson's disease. Am J Epidemiol 144:480–484
16. de Lau LM, Koudstaal PJ, Hofman A, Breteler MM (2005) Serum uric acid levels and the risk of Parkinson disease. Ann Neurol 58:797–800
17. Zoccolella S, Simone IL, Capozzo R, Tortelli R, Leo A, D'Errico E, Logroscino G (2011) An exploratory study of serum urate levels in patients with amyotrophic lateral sclerosis. J Neurol 258:238–243
18. Keizman D, Ish-Shalom M, Berliner S, Maimon N, Vered Y, Artamonov I, Tsehori J, Nefussy B, Drory VE (2009) Low uric acid levels in serum of patients with ALS: further evidence for oxidative stress? J Neurol Sci 285:95–99
19. Weisskopf MG, O'Reilly E, Chen H, Schwarzschild MA, Ascherio A (2007) Plasma urate and risk of Parkinson's disease. Am J Epidemiol 166:561–567
20. Alonso A, Rodriguez LA, Logroscino G, Hernan MA (2007) Gout and risk of Parkinson disease: a prospective study. Neurology 69:1696–1700
21. Andreadou E, Nikolaou C, Gournaras F, Rentzos M, Boufidou F, Tsoutsou A, Zournas C, Zissimopoulos V, Vassilopoulos D (2009) Serum uric acid levels in patients with Parkinson's disease: their relationship to treatment and disease duration. Clin Neurol Neurosurg 111:724–728
22. Paganoni S, Zhang M, Quiroz Zarate A, Jaffa M, Yu H, Cudkowicz ME, Wills AM (2012) Uric acid levels predict survival in men with amyotrophic lateral sclerosis. J Neurol 259(9):1923–1928
23. Ascherio A, LeWitt PA, Xu K, Eberly S, Watts A, Matson WR, Marras C, Kieburtz K, Rudolph A, Bogdanov MB, Schwid SR, Tennis M, Tanner CM, Beal MF, Lang AE, Oakes D, Fahn S, Shoulson I, Schwarzschild MA (2009) Urate as a predictor of the rate of clinical decline in Parkinson disease. Arch Neurol 66:1460–1468
24. Schwarzschild MA, Schwid SR, Marek K, Watts A, Lang AE, Oakes D, Shoulson I, Ascherio A, Hyson C, Gorbold E, Rudolph A, Kieburtz K, Fahn S, Gauger L, Goetz C, Seibyl J, Forrest M, Ondrasik J (2008) Serum urate as a predictor of clinical and radiographic progression in Parkinson disease. Arch Neurol 65:716–723
25. Lee JE, Song SK, Sohn YH, Lee PH (2011) Uric acid as a potential disease modifier in patients with multiple system atrophy. Mov Disord 26:1533–1536
26. Kim HJ, Jeon BS, Lee JY (2011) Serum urate levels are not associated with survival in multiple system atrophy. Parkinsonism Relat Disord 17:400–401
27. Wenning GK, Tison F, Seppi K, Sampaio C, Diem A, Yekhlef F, Ghorayeb I, Ory F, Galitzky M, Scaravilli T, Bozi M, Colosimo C, Gilman S, Shults CW, Quinn NP, Rascol O, Poewe W (2004) Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). Mov Disord 19:1391–1402
28. Zhang X-j, Wu Y-w, Chen S-d (2007) Application of UMSARS-1 in evaluation of illness severity in patients with multiple system atrophy. Journal of Shanghai Jiaotong Univ (Med Sci) 27:706–709
29. Squadrito GL, Cueto R, Splenser AE, Valavanidis A, Zhang H, Uppu RM, Pryor WA (2000) Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. Arch Biochem Biophys 376:333–337
30. Davies KJ, Sevanian A, Muakkassah-Kelly SF, Hochstein P (1986) Uric acid-iron ion complexes. A new aspect of the antioxidant functions of uric acid. Biochem J 235:747–754
31. Einsele H, Clemens MR, Wegner U, Waller HD (1987) Effect of free radical scavengers and metal ion chelators on hydrogen peroxide and phenylhydrazine induced red blood cell lipid peroxidation. Free Radic Res Commun 3:257–263
32. Miura T, Muraoka S, Ogiso T (1993) Inhibitory effect of urate on oxidative damage induced by adriamycin-$Fe_3{}^+$in the presence of H_2O_2. Res Commun Chem Pathol Pharmacol 79:75–85
33. Vanacore N, Bonifati V, Fabbrini G, Colosimo C, Marconi R, Nicholl D, Bonuccelli U, Stocchi F, Lamberti P, Volpe G, De Michele G, Iavarone I, Bennett P, Vieregge P, Meco G (2000) Smoking habits in multiple system atrophy and progressive supranuclear palsy. European study group on atypical Parkinsonisms. Neurology 54:114–119
34. Seo JH, Yong SW, Song SK, Lee JE, Sohn YH, Lee PH (2010) A case-control study of multiple system atrophy in Korean patients. Mov Disord 25:1953–1959