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Short communication

Prevalence of and factors associated with postural deformities in Chinese patients with multiple system atrophy

LingYu Zhang[a], Bei Cao[a], Yutong Zou[b], Qian-Qian Wei[a], RuWei Ou[a], Bi Zhao[a], Jing Yang[a], Ying Wu[a], HuiFang Shang[a,*]

[a] Department of Neurology and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China
[b] West China School of Medicine, Sichuan University, Chengdu, Sichuan, China

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ABSTRACT

Objective: The prevalence of postural deformities in patients with multiple system atrophy (MSA) has varied among previous studies. The objective of our study was to investigate the prevalence of and factors associated with postural deformities in Chinese MSA patients.

Methods: A total of 732 MSA patients were consecutively enrolled in the current study. Clinical data including age, sex, age of onset, disease duration, onset symptom and treatment were collected. The Unified Multiple System Atrophy Rating Scale (UMSARS) was used to evaluate the severity of the disease.

Results: One hundred and fourteen (15.6%) patients presented with camptocormia. Thirty-one (4.2%) patients manifested with Pisa syndrome. Twenty-four (3.3%) patients presented with antecollis. Patients who exhibited postural deformities were more common among the MSA patients with predominant parkinsonism (MSA-P) ($P < 0.05$). In addition, MSA patients with postural deformities had a longer disease duration compared to those patients without postural deformities ($P < 0.001$). After adjusting for disease duration, compared with patients without postural deformities, MSA patients with postural deformities presented with higher score of UMSARS-I ($P < 0.001$), UMSARS-II ($P < 0.001$), UMSARS-IV ($P < 0.001$), and total UMSARS ($P < 0.001$) scores. The binary logistic regression model indicated that the factors associated with postural deformity in MSA patients were the total UMSARS score (OR = 1.076, $P < 0.001$) and MSA-P subtype (OR = 3.870, $P < 0.001$).

Conclusion: Postural deformities were common in Chinese MSA patients. Camptocormia was the most common type of postural deformity, followed by Pisa syndrome and antecollis. The factors associated with postural deformity were the severity of the disease and MSA-P subtype.

1. Introduction

Postural deformities, including camptocormia, disproportionate antecollis, and Pisa syndrome, have been reported to be seen in multiple system atrophy (MSA) [1,2]. Although there have been some case reports [1] and small sample size studies [3], large sample studies on postural deformities of MSA are few. Furthermore, due to the small sample size of those studies, the prevalence of antecollis in MSA varied from 4% to 42.1% [4,5], and the prevalence of truncal dystonia in MSA varied from 2.0% to 42.1% [2,6]. To date, there has been no study available on the prevalence of postural deformities in Chinese MSA patients.

Postural deformities may reduce dexterity, impose restrictions on activities of daily living, disrupt gait, increase falls, and produce pain or discomfort [4]. Furthermore, the pathophysiology of postural deformities is largely unknown, although it may be related to muscular rigidity, axial dystonia, weakness caused by myopathy, and structural changes in the spine [7]. A better understanding the signs of postural deformities in MSA is very important for management of the disease. Hence, we aimed to perform a large sample study to investigate the prevalence of and factors associated with postural deformities in MSA patients in a Chinese population.

2. Patients and methods

A total of 1001 patient with MSA were consecutively recruited from the Department of Neurology, West China Hospital of Sichuan University, between May 2011 and June 2018 after approval was

* Corresponding author. Department of Neurology and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China.
E-mail address: hfshang2002@126.com (H. Shang).

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Table 1
Demographic and clinical features of the MSA patients with and without camptocormia, Pisa syndrome, and antecollis.

Variables	With camptocormia	Without camptocormia	P value	With Pisa syndrome	Without Pisa syndrome	P value	With antecollis	Without antecollis	P value
Number N (%)	114(15.6%)	618(84.4%)	–	31 (4.2%)	701 (95.8%)	–	24 (3.3%)	708 (96.7%)	–
Subtype (MSA-P/ MSA-C)	86/28 75.4%/24.6%	247/371 40.0%/60.0%	< 0.001*	28/3 90.3%/9.7%	305/396 43.5%/56.5%	< 0.001*	20/4 83.3%/16.7%	313/395 44.2%/55.8%	< 0.001*
Male/Female	49/65 44.0%/57.0%	321/297 51.9%/48.1%	0.079	15/16 48.4%/51.6%	355/346 50.6%/49.4%	0.806	7/17 29.2%/70.8%	363/345 51.3%/48.7%	0.033*
Mean age (years)	61.10 ± 8.08	59.59 ± 8.56	0.082	58.04 ± 8.07	59.91 ± 8.51	0.309	61.20 ± 7.25	59.78 ± 8.54	0.409
Age of onset (years)	57.64 ± 8.41	56.95 ± 8.51	0.428	54.02 ± 8.57	57.19 ± 8.47	0.070	57.22 ± 7.85	57.05 ± 8.52	0.945
Disease duration (years)	3.92 ± 1.69	2.64 ± 1.46	< 0.001*	4.21 ± 1.92	2.78 ± 1.52	< 0.001*	4.39 ± 1.49	2.79 ± 1.54	< 0.001*
Combined motor and autonomic involvement within 3 years of onset									
Yes/no	90/24	507/111	0.434	23/8	574/127	0.280	22/2	575/133	0.194
Early generalized autonomic failure within 3 years of onset									
Yes/no	49/65	318/300	0.096	15/16	352/349	0.842	10/14	357/351	0.399
Symptom onset									
Motor onset	56(49.1%)	338(54.7%)	0.273	17(54.8%)	377(53.8%)	0.908	15(62.5%)	379(53.5%)	0.386
Autonomic onset	58(50.9%)	280(45.3%)		14(45.2%)	324(46.2%)		9(37.5%)	329(46.5%)	
UMSARS-I	27.54 ± 8.91	17.90 ± 7.17	< 0.001*	28.87 ± 8.51	18.98 ± 7.98	< 0.001*	29.37 ± 9.09	19.06 ± 8.00	< 0.001*
UMSARS-II	29.95 ± 9.58	19.46 ± 7.80	< 0.001*	31.26 ± 8.84	20.65 ± 8.68	< 0.001*	32.04 ± 10.79	20.72 ± 8.64	< 0.001*
UMSARS-IV	3.29 ± 1.16	2.21 ± 1.04	< 0.001*	3.52 ± 1.24	2.33 ± 1.10	< 0.001*	3.79 ± 1.06	2.33 ± 1.10	< 0.001*
Total UMSARS score	60.78 ± 18.66	39.57 ± 14.96	< 0.001*	63.65 ± 17.21	41.96 ± 16.81	< 0.001*	65.21 ± 20.07	42.12 ± 16.78	< 0.001*
Treatment									
Levodopa	63(55.3%)	172(27.8%)	< 0.001*	19(61.3%)	216(30.8%)	< 0.001*	18(75.0%)	217(30.6%)	< 0.001*
Dopamine receptor agonist	31(27.2%)	77(12.5%)	< 0.001*	10(32.3%)	98(14.0%)	0.011*	9(37.5%)	99(14.0%)	0.004*
Amantadine	24(21.1%)	69(11.2%)	0.004*	8(25.8%)	85(12.1%)	0.050	6(25.0%)	87(12.3%)	0.127
Buspirone hydrochloride	21(18.4%)	23(3.7%)	< 0.001*	3(9.7%)	41(5.8%)	0.623	2(8.3%)	42(5.9%)	0.960

MSA, multiple system atrophy; MSA-P, multiple system atrophy with predominately parkinsonism; MSA-C, multiple system atrophy with predominately cerebellar ataxia; UMSARS, unified multiple system atrophy rating scale.
* Significant difference.

obtained from the Ethics Committee of West China Hospital of Sichuan University. Two hundred and sixty-nine patients including who met the "possible" diagnosis of MSA [8] or who had incompletely data were excluded from the current study. The remaining 732 probable MSA patients were included in the data analysis. All subjects signed informed consent forms.

MSA patients with predominantly parkinsonian features were designated MSA-P, and patients with predominantly cerebellar ataxia were designated MSA-C. Patients were screened for spinocerebellar ataxia (SCA) genes, including SCA1, 2, 3, 6, and 7, to exclude the common forms of SCA. Clinical data including age, sex, age of onset, disease duration, onset symptoms and treatment were collected by professional neurologists via a face-to-face interview. Disease duration was defined as the time from disease onset date to the evaluation date. Disease onset referred to the initial presentation of any motor problems (whether parkinsonism or cerebellar) or autonomic features, with the exception of male erectile dysfunction [8]. The Unified Multiple System Atrophy Rating Scale (UMSARS) was used to evaluate the disease severity.

Camptocormia is defined as a distinctive and much more pronounced manifestation of this stooped posture, with flexion originating in the thoracic or lumbar spine [7]. Pisa syndrome requires pronounced (at least 10°) lateral flexion, which can be alleviated completely by passive mobilization or by lying supine [7]. Antecollis refers to a forward flexion of the head and neck [7].

3. Statistical analysis

All continuous data are presented as the mean ± standard deviation. All categorical variables are presented as numbers or percentages. The Mann–Whitney *U* test was performed to compare the continuous variables between MSA patients with and without postural deformities. Chi-square test was implemented to analyze the differences in categorical data between MSA patients with and without postural deformities. UMSARS-I, UMSARS-II, UMSARS-IV, and total UMSARS scores were compared between the MSA patients with and without postural deformities by analyses of covariance (ANCOVA) with adjustment for disease duration. To explore the factors associated with postural deformity in MSA patients, we used the binary logistic regression model. The presence or absence of postural deformity was used as a dependent variable in this analysis to identify potentially related factors. The diagnosis subtype, sex, age, disease duration, and UMSARS-I, UMSARS-II, UMSARS-IV, and total UMSARS scores were considered covariables. All the data analyses were performed using SPSS 22.0 (IBM, Chi-cago, IL). A value of $P < 0.05$ was considered statistically significant.

4. Results

Among all 732 enrolled patients, 114 (15.6%) patients presented with camptocormia, 31 (4.2%) patients presented with Pisa syndrome, and 24 (3.3%) patients presented with antecollis at the time of evaluation. Demographic and clinical features of MSA patients are shown in Supplementary Table A. The comparisons between MSA-C patients with and without postural deformities and between MSA-P patients with and without postural deformities are shown in Supplementary Tables B and C.

We found that the patients with camptocormia were more common among MSA-P patients than among MSA-C patients ($P < 0.001$). The mean disease duration of the MSA patients with camptocormia was significantly longer than those MSA patients without camptocormia (3.92 ± 1.69 vs 2.64 ± 1.46, $P < 0.001$). After adjusting for disease duration, patients with camptocormia had higher scores of UMSARS-I ($P < 0.001$), UMSARS-II ($P < 0.001$), UMSARS-IV ($P < 0.001$), and total UMSARS scores ($P < 0.001$) than those patients without camptocormia. The proportion of drug use (levodopa, dopamine receptor

agonist, amantadine, and buspirone hydrochloride) was higher in patients with camptocormia than in those patients without camptocormia ($P < 0.05$). (Table 1).

Pisa syndrome was more frequently observed in MSA-P patients than in MSA-C patients ($P < 0.001$). Compared to patients without Pisa syndrome, patients with Pisa syndrome had a longer disease duration (4.21 ± 1.92 vs 2.78 ± 1.52, $P < 0.001$). After adjusting for disease duration, MSA patients with Pisa syndrome had higher score of UMSARS-I ($P < 0.001$), UMSARS-II ($P < 0.001$), UMSARS-IV ($P < 0.001$), and total UMSARS scores ($P < 0.001$) than those without Pisa syndrome. The proportion of drug use was higher in patients with Pisa syndrome than in those patients without Pisa syndrome ($P < 0.05$). (Table 1).

As shown in Table 1, patients with antecollis most often presented as the MSA-P subtype ($P < 0.001$). In terms of sex differences, antecollis was more frequently in females than in males among MSA patients ($P = 0.033$). The MSA patients with antecollis had a significantly longer disease duration than those MSA patients without antecollis (4.39 ± 1.49 vs 2.79 ± 1.54, $P < 0.001$). After adjusting for disease duration, MSA patients with antecollis had higher score of UMSARS-I ($P < 0.001$), UMSARS-II ($P < 0.001$), UMSARS-IV ($P < 0.001$), and total UMSARS scores ($P < 0.001$) than those MSA patients without antecollis. The proportion of drug use was higher in patients with antecollis compared to those without ($P < 0.05$).

In the binary logistic regression model (Table 2). We found that the MSA-P subtype (OR = 3.870, 95%CI = 2.396–6.250, $P < 0.001$) and total UMSARS score (OR = 1.076, 95%CI = 1.061–1.091, $P < 0.001$) were associated with postural deformity in MSA patients. The sex, age, disease duration, and UMSARS-I, UMSARS-II, and UMSARS-IV scores did not have significant associations with postural deformity.

5. Discussion

In the current study, we focused on the postural deformities of camptocormia, Pisa syndrome, and antecollis, which are considered “red flags” for supporting the diagnosis of MSA [8]. This is the first large study to investigate the prevalence of and factors associated with postural deformities in a Chinese MSA population. The prevalence of postural deformities in the MSA patients with an average disease duration of 2.85 ± 1.57 years was 18.6% in this study. The most common form of postural deformity in MSA was camptocormia (15.6%) followed by Pisa syndrome (4.2%), and antecollis (3.3%). The MSA-P subtype and disease severity, but not disease duration, were factors associated with postural deformity in MSA patients.

In our study, camptocormia occurred in 15.6% of the MSA patients; this finding was lower than that of an American study (26.3%, 5/19) [4]. However, the sample size of the American retrospective study was too small [4]. The prevalence of Pisa syndrome in the MSA patients was 4.2% in the current study. Previous studies that focused on Pisa syndrome in MSA patients were almost all case reports. Only one European study showed that the prevalence of 42.1% of Pisa syndrome in 57 MSA-P patients with a mean disease duration of 4.9 ± 3.8 years [6]. Our study found that Pisa syndrome was presented in 8.4% (28/333) of MSA-P patients. Antecollis occurred in 3.3% of our MSA patients at the time of evaluation, and this result was similar to the finding of a Japanese study (4%) [5] and a European study (5%), which evaluated a large sample of 203 pathologically proven MSA cases [2]. Thus, this discrepancy in the frequency of postural deformities may mainly be due to the small sample sizes of previous studies as well as the difference in the severity of the disease among different studies.

Table 2
Factors associated with postural deformity in MSA patients.

Variable	OR	95%CI	P value
Diagnosis subtype	3.870	2.396–6.250	< 0.001*
Total UMSARS score	1.076	1.061–1.091	< 0.001*

MSA, multiple system atrophy; UMSARS, unified multiple system atrophy rating scale.
* Significant difference.

Furthermore, we found that MSA patients with postural deformities (camptocormia, Pisa syndrome, and antecollis) were more common in the MSA-P subtype, which may be due to a basal ganglia pathology as a possible pathogenesis of the postural deformities [9]. We found that antecollis was more common in female MSA patients. A Japanese study on Parkinson's disease (PD) patients with dropped head syndrome showed that dropped head syndrome were more often observed in women [10], which also supports our results. However, the mechanism by which antecollis is more commonly seen in females remains unclear. Further study is needed to verify this finding. We first found that the disease severity of MSA patients with postural deformities (camptocormia, Pisa syndrome, and antecollis) was severer than that of those MSA patients without postural deformities, which indicates that postural deformities are more likely to represent the severity of pathology of the disease, and may be markers of disease progression. Our previous study found that the PD patients with camptocormia had more severe motor disabilities [11], which may also support our current findings since PD and MSA are alpha-synuclein neuropathy diseases. In addition to disease severity, we found that the MSA-P subtype is a factor associated with postural deformities in MSA, which may result from the fact that the deficit of the striatum in the MSA-P subtype was more severe than that in the MSA-C subtype. However, studies on the pathophysiology of postural deformities have suggested the involvement of complicated mechanisms. The possible pathogenesis of camptocormia includes a form of dystonia; a consequence of paraspinal myopathy and caused by medications. A previous study has reported that the possible pathophysiology of Pisa syndrome was involved with multiple factors, including asymmetric basal ganglia function, impaired processing of sensory information, cognitive dysfunction, and altered perception of body alignment [9]. In addition, although the mechanism of antecollis remains unclear, multiple hypotheses have been proposed to explain its underlying aetiology, including myopathy, dystonia, weakness in the neck extensor musculature, and disproportionate rigidity and so on.

In our current study, we compared the drug use between the MSA patients with and without postural deformities. We found that the proportion of drug use was higher in patients with postural deformities than in those patients without, which may be due to the fact that the patients with postural deformities had more severe disease. Drug-induced postural deformities in patients with MSA can also arise from an increase or decrease in the dose of dopamine receptor agonist or dopaminergic treatment. The mechanism is unclear, but a proposed mechanism is the presence of an imbalance among dopamine, norepinephrine, and serotonin levels, and the way in which these neurotransmitters regulate axial muscle tone [12]. However, notably, most of those studies were only case reports with weak evidence, and most patients taking dopamine receptor agonists or levodopa do not develop postural deformities. In the current study, although we cannot exclude the effects of drugs, the possibility of a drug effect is small.

There were some limitations that cannot be ignored in the present study. First, this is a cross-sectional study. A longitudinal study is needed to elucidate the development of postural deformities during different disease stages in the future. In addition, we only used the UMSARS to assess the motor symptoms of the MSA patients. Using other scales such as the non-motor symptoms scale (NMSS) can help us to obtain a comprehensive understanding of the characteristics of the MSA patients with postural deformities.

6. Conclusion

Postural deformities are common in MSA patients, and camptocormia is the most common postural deformity, especially in MSA-P

patients. The MSA-P subtype and more severe disease were associated with postural deformities in MSA patients.

Conflicts of interest

The authors declare that there was no potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.03.024.

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