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Original Articles

Serum uric acid level is linked to the disease progression rate in male patients with multiple system atrophy

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ABSTRACT

Objectives: Multiple system atrophy (MSA) is a progressive neurodegenerative disorder that may be caused in part by oxidative stress. Uric acid (UA) protects neurons in neurodegenerative disorders via antioxidative effects. The aim of this study was to investigate the relationship between the serum UA concentration and disease progression in MSA patients.

Patients and methods: A total of 53 Japanese MSA patients were enrolled in this study. The disease progression rate was estimated by the rate of global disability scale change per year. The relationship between the serum UA concentration and disease progression was assessed by Spearman's correlation analysis. Disease progression depending on the UA concentration was also estimated by multivariate logistic regression analysis.

Results: MSA patients with the highest serum UA concentration had lower disease progression rates than those with the lowest concentration. Spearman's correlation analysis showed an inverse correlation between the serum UA concentration and disease progression in male patients. Multivariate logistic regression analysis confirmed that the UA concentration was independently related to disease progression only in male patients.

Conclusion: These results suggest that serum UA may be associated with disease progression in male patients with MSA.

1. Introduction

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder that encompasses three syndromes previously considered to be separate disorders: striatonigral degeneration, olivopontocerebellar atrophy, and Shy-Drager syndrome. According to a consensus statement on MSA diagnosis, predominately parkinsonian features are associated with the MSA-P subtype, whereas predominately cerebellar features are associated with the MSA-C subtype [1]. Although the cause of MSA is still unknown, genetic and immunohistological evidence suggests that oxidative stress contributes to MSA pathogenesis [2–4].

Previous studies indicate that uric acid (UA) can protect neurons against neurodegeneration by exerting antioxidative effects. For instance, a higher serum UA concentration reduces the risk of Parkinson's disease onset and slows progression of the disease [5,6], and the serum UA concentration is linked to the progression of other neurodegenerative disorders such as Huntington's disease and amyotrophic lateral sclerosis [7,8]. However, the role of UA in MSA is not well understood. Although some previous studies reported that the serum UA concentration was not associated with MSA progression or survival [9,10], others reported that the serum UA concentration was correlated with MSA occurrence and progression [10–12]. Therefore, we examined whether the serum UA concentration was linked to disease progression in MSA patients.

2. Material and methods

2.1. Subjects

A total of 53 Japanese MSA patients were enrolled in this study. These patients were admitted, and their clinical symptoms were evaluated in the Department of Neurology, Fukuoka University Hospital or Juntendo University Hospital between January 2009 and March 2015. MSA was diagnosed according to the second consensus criteria [13], and all patients enrolled in this study had clinically probable MSA. The enrolled patients were all inpatients at baseline, and diagnosis of MSA was confirmed by more than two expert neurologists. Key exclusion criteria were severe dementia, psychiatric symptoms, and

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severe complications such as pneumonia, bone fracture, and advanced-stage cancer. The study was approved by the Fukuoka University and Juntendo University committees for medical research ethics and followed the principles outlined in the Declaration of Helsinki.

Blood samples for laboratory analysis including the serum UA concentration were obtained from all subjects between 5:00-7:00 am, following about 8 h of fasting. Venous blood samples (9 ml) were taken from each MSA patient, and then serum was separated within the hour by centrifugation at 3500 rpm for 6 min. The serum UA concentration was measured with enzymatic methods (Labospect008, Hitachi, Tokyo, Japan). To evaluate the general condition, the following data were retrospectively obtained from all subjects by inquiry and physical and laboratory examinations: age, sex, history of hypertension and diabetes mellitus, body mass index (BMI, kg/m^2), total cholesterol (T-cho; mg/dL), low-density lipoprotein cholesterol (LDL-C; mg/dL), and triglycerides (TG; mg/dL).

2.2. Assessment of MSA

The clinical severity of MSA was evaluated with the global disability scale (GDS) in the Unified Multiple System Atrophy Rating Scale (UMSARS part IV) [14]. The information about MSA patients, such as the UA concentration and disease duration, was not disclosed to evaluators of GDS. The average disease progression rate was defined as a GDS (UMSARS part IV) change per one year, which was calculated using the following formula:

Disease progression rate = GDS (UMSARS part IV)/disease duration (years)

2.3. Data analysis

Statistical analyses were performed using SPSS software package version 21 (SPSS Inc., Chicago, IL, USA) for Macintosh. The UA concentrations of all subjects were divided into tertiles to minimize the influence of any extreme observation on the results (group 1, low UA concentration: ≤4.0 mg/dL; group 2, moderate UA concentration: 4.1–5.0 mg/dL; group 3, high UA concentration: ≥5.1 mg/dL). Differences in clinical and demographic characteristics were evaluated using Fisher's exact test and one-way analysis of variance. To evaluate the trend in the mean average disease progression rate by groups, the Jonckheere–Terpstra trend test was performed. In addition, the correlation between the disease progression rate and serum UA concentration was evaluated by Spearman's correlation analysis. The average disease progression rate was divided into two groups. Rapid disease progression was defined as one or more than one stage change per year, and slow progression as less than one stage change per year. To determine the independent association between the serum UA concentration and rapid disease progression, multivariable stepwise logistic regression was performed (covariates were removed if $p > 0.1$ and entered if $p < 0.05$). Adjusted odds ratios (ORs) and 95% confidence intervals (CI) for each group were compared. The following covariates were included based on their biological plausibility or evidence from the literature: age, sex, age of onset, disease duration, daily levodopa dose, GDS, BMI, T-cho, LDL-C, and TG. Considering the relationship between the UA concentration and sex, we also repeated the analysis using sex-specific UA concentration tertiles (males: group 1, ≤4.4 mg/dL; group 2, 4.5–5.4 mg/dL; group 3, ≥5.5 mg/dL; females: group 1, ≤3.3 mg/dL; group 2, 3.4–4.3 mg/dL; group 3, ≥4.4 mg/dL). A p-value < 0.05 was deemed statistically significant.

3. Results

Clinical, laboratory, and medication data for each group of MSA patients are presented in Table 1. The mean age of all subjects was 65.45 ± 8.63 years. The mean serum UA concentration was 4.62 ± 1.30 mg/dL. The subjects included 30 patients with MSA-C (56.6%) and 23 with MSA-P (43.4%). BMI, T-cho, and TG were significantly increased with an increase in the serum UA concentration. No significant differences in age, age of onset, disease duration, GDS, LDL-C, or medication except levodopa were noted among the UA groups.

The average disease progression rate was not different according to sex or age of onset (men, 1.06 ± 0.76; women, 1.02 ± 0.46; $p = 0.821$) (age of onset ≤61 years, 1.03 ± 0.43; age of onset ≥62 years, 1.05 ± 0.75; $p = 0.944$). The average disease progression rate of MSA-P was slightly higher than that of MSA-C (MSA-C, 0.93 ± 0.48; MSA-P, 1.18 ± 0.74; $p = 0.150$). The average disease progression rates for each UA group were not significantly different (group 1, 1.24 ± 0.82; group 2, 0.98 ± 0.38; group 3, 0.78 ± 0.41, $p = 0.085$) (Table 1). We observed a tendency in which the average disease progression rate decreased with an increasing serum UA concentration in all subjects (p for trend = 0.008).

To evaluate the correlations between disease progression and the serum UA concentration, we performed Spearman's correlation analysis. In all subjects, the serum UA concentration showed a mild inverse correlation with average disease progression ($r_s = -0.326$, $p = 0.017$) (Fig. 1). For sex, we observed a significant correlation between the serum UA concentration and average disease progression only in male patients (males; $r_s = -0.419$, $p = 0.037$, females; $r_s = -0.183$, $p = 0.352$) (Fig. 1). For the type of disease, no significant correlation was observed between the serum UA concentration and average disease progression rate (MSA-C; $r_s = -0.170$, $p = 0.369$, MSA-P; $r_s = -0.361$, $p = 0.091$). For disease duration, we observed a significant correlation between the serum UA concentration and average disease progression only in patients with short disease duration (short duration [≤3 years]; $r_s = -0.527$, $p = 0.002$, long duration [> 3 years]; $r_s = -0.163$, $p = 0.437$).

Adjusted ORs for rapid disease progression after adjusting for other potential confounders are shown in Table 2. When patients were divided by sex, the association between the UA group and the average disease progression rate was significant only among males (ORs of high UA concentration, 0.021; 95% CI, 0.001–0.704; $p = 0.031$). In addition, BMI (OR 0.637, 95% CI, 0.452–0.897, $p = 0.01$) was independently associated with rapid disease progression. Other covariates including the daily levodopa dose were not associated with rapid disease progression in MSA patients.

4. Discussion

In this retrospective study, we found that the serum UA concentration was inversely associated with disease progression in male MSA patients. In addition, multivariable logistic regression analysis demonstrated that the OR of rapid disease progression in the highest serum UA group was significantly lower than that in the lowest serum UA group only in male patients with MSA.

Patients with MSA show various symptoms, and several previous clinical studies have reported associations between disease occurrence, disease progression, survival, and cognitive function in MSA patients and the serum UA concentration [9–12,15]. Two cross-sectional studies demonstrated that the occurrence of MSA was decreased in patients with a high UA concentration, especially in male patients [10,12]. Regarding the link between survival and the serum UA concentration in MSA patients, Kim et al. found no association between survival and serum UA in MSA patients [9]. Another report demonstrated that the UA concentration is inversely associated with cognitive deficits in MSA patients [15].

Two previous reports investigated disease progression and the serum UA concentration in MSA patients. These two reports showed different conclusions. First, a prospective study evaluated the influence of the serum UA concentration on disease progression in 52 MSA