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ORIGINAL COMMUNICATION

Serum uric acid levels and neuromyelitis optica

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Abstract Uric acid (UA) has been reported to be reduced in the serum of patients with multiple sclerosis (MS) and optic neuritis (ON). However, the relationship between UA and neuromyelitis optica (NMO) was unknown. NMO was claimed to be a distinct nosologic entity from MS. The aim of our study was to investigate the correlation between serum UA level and the clinical characteristics of NMO. The serum UA level was measured in 403 Chinese patients; 69 with NMO, 32 ON, 127 MS, 80 cerebral infarction (CI) patients, and 95 healthy controls (CTL). Serum UA level in NMO was significantly lower than that in CI (249.89 ± 93.74 vs. 315.42 ± 85.57 μmol/L, $p = 0.004$) and CTL (249.89 ± 93.74 vs. 314.33 ± 102.05 μmol/L, $p < 0.0001$). However, no difference was found between NMO and MS ($p = 0.496$) or NMO and ON ($p = 0.858$). When the analysis was performed in the female cohort separately, UA level was significantly lower in females than in males in all groups. It was also shown in our study that UA level in patients with NMO was not correlated with disease activity revealed by MRI, disease disability or duration of disease. Our results indicated a reduced serum UA level in patients with NMO.

Keywords Uric acid · Neuromyelitis optica · Multiple sclerosis · Peroxynitrite

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Introduction

Uric acid (UA) is the end product of purine metabolism. Being a scavenger of peroxynitrite (PN), UA accounts for up to 60% of the free radical scavenging activity in human blood [1, 2]. In experimental allergic encephalomyelitis (EAE), a prototypical animal model of multiple sclerosis (MS), UA was found to be able to suppress the inflammatory cascade, decrease blood–brain barrier permeability, and diminish central nervous tissue damage and neuronal death [3]. Numerous evidences have also showed that treatment with UA promoted the recovery of neurological function in mice with EAE [1, 4]. Inosine, a UA precursor, has a similar therapeutic effect on EAE [5].

Neuromyelitis optica (NMO) is an immune mediated disease which selectively targets the optic nerves and spinal cord and spares the brain in the early stage [6]. Although there is a debate on whether NMO is a distinct nosologic entity or a variant of MS, NMO does distinguish from MS in the clinical, imaging, serological and immunopathological profiles [7].

A reduced serum UA level has been reported in patients with MS and optic neuritis (ON) by us and others [8–11]. Furthermore, UA has been considered as a surrogate marker of MS activity [12]. However, the relationship between UA and NMO has not been investigated.

Therefore, we performed a hospitalized-based study to investigate the correlation between serum UA level and clinical characteristics of patients with NMO including disease duration, disease disability assessed by the Expanded Disability Status Scale (EDSS) score [13] and disease activity on magnetic resonance imaging (MRI). To our knowledge, this was the first clinical study on UA in patients with NMO.

Patients and methods

Serum samples were collected from 403 Chinese individuals with NMO, ON, MS, cerebral infarction (CI) and healthy controls (CTL). All patients had been hospitalized and had confirmed diagnosis according to the different disease diagnostic criteria. Demographic and clinical characteristics of the patients and healthy control group were summarized in Table 1. The mean durations of NMO, MS and ON patients were, respectively, 2.01 ± 3.40 years (range 0.01–17.00 years), 1.38 ± 1.93 years (range 0.10–11.00 years) and 21.98 ± 68.66 months (range 0.01–330 months). The mean ages at disease onset of NMO, MS and ON patients were, respectively, 31.52 ± 13.07 years (range 8.90–63.90 years), 33.06 ± 14.02 years (range 3.70–65.00 years) and 31.64 ± 18.02 years (6.41–64.92 range years).

Neuromyelitis optica patients were diagnosed on the revised 2006 criteria [14] and MS patients had clinical definite MS on the criteria of Poser et al. [15] or McDonald et al. [16]. We have tested our 58 NMO patients for the presence of anti-AQP4 antibodies by anti-AQP4 antibody assay on an AQP4-transfected cell line from a commercial kit of BIOCHIP (EUROIMMUN company, Germany). There were 33 patients with the positive presence of anti-AQP4 antibodies; another 25 patients presented the negative. NMO and MS patients were scored by the EDSS [13]. Most reasons for hospitalization were for diagnostic or therapeutic purposes in patients with clinically active disease (defined as the development within the previous 2 weeks of new neurological symptoms or signs attributable to demyelination). Patients with ON were diagnosed after brain and spinal cord MRI were performed in order to exclude the possibility of MS or NMO.

Patients with NMO were further subdivided into two groups: group 1 of 39 patients with spinal cord activity on MRI and group 2 of 19 patients without spinal cord activity. NMO was considered to be active on MRI if there were one or more enhancing lesions in T1-weighted spin-echo images post gadopentate dimeglumine (Gd-DTPA) injection. Gd-DTPA was given intravenously at a dose 0.1 mmol/kg and about 15 min after contrast injection the T1-weighted sequence was repeated.

All patients and control subjects completed a diet questionnaire. Blood was drawn by venepuncture after an overnight fasting. Exclusion criteria included treatment with steroids, acetylsalicylic acid, thiazide diuretics, ibuprofen and other drugs that could increase or affect UA levels, as well as subjects with diabetes or renal failure. Before blood was drawn for the present study, some patients were treated with glucocorticoids. The numbers of NMO, MS and ON patients treated with glucocorticoids were, respectively, 18, 15 and 11.

UA concentration was measured by the direct enzymatic method, in which uric acid was oxidized by uricase coupled with peroxidase. Serum uric acid was measured using a Clinical Analyzer 7180-ISE (Hitachi High-Technologies, Tokyo, Japan). In our hospital, the normal range of serum UA values is 150–360 μmol/L in women and 210–430 μmol/L in men.

Statistical analysis

All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS) statistical software (version 17.0, Chicago, IL, USA). All the data in this study are presented as mean ± SD. Statistical significance was set at $p < 0.05$. The effect of age and gender on serum UA levels of different groups were analyzed by covariance analysis. The comparison between serum UA levels of the patients and the control subjects were performed using covariance analysis with age as covariant. Since serum UA

Table 1 Demographic characteristics of the patients and healthy controls

Subjects	Total no. of patients	No. of male	No. of female	Mean of ages (range), years
Neuromyelitis optica	69	19	50	33.54 (9–65)
Optic neuritis	32	12	20	34.66 (7–66)
Multiple sclerosis	127	48	79	34.41 (4–68)
Cerebral infarction	80	32	48	53.33 (29–92)
Healthy controls	95	47	48	40.58 (20–68)

levels have been shown to be dependent on gender, in order to eliminate the effect of gender, patients with each group were divided into two subgroups according to gender. Covariance analysis was also used to compare serum UA levels of male and female patients or the control subjects with age as covariant.

Results

Demographic characteristics of the patients and the control group were presented in Table 1. The mean EDSS score in NMO group was 4.6 ± 2.3 (range 1–8.5) and the mean duration of disease was 34.6 ± 50.4 months.

As shown in Tables 2, 3 and Fig 1, the mean serum UA level in all participants was 274.99 ± 102.05 μmol/L. Serum UA level in NMO was significantly lower compared to that in CI (249.89 ± 93.74 vs. 315.42 ± 85.57 μmol/L, $p = 0.004$) and CTL (249.89 ± 93.74 vs. 314.33 ± 102.05 μmol/L, $p < 0.0001$). However, no difference was found between NMO and MS ($p = 0.496$) or NMO and ON ($p = 0.858$).

As serum UA level has been shown to be dependent on gender, we further subdivided each diagnostic group of patients into two subgroups stratified by gender. In all diagnostic groups, females had significantly lower serum UA level than males ($p < 0.05$). UA level in female NMO was also significantly lower compared to that in female CI (218.68 ± 75.30 vs. 293.48 ± 71.94 μmol/L, $p = 0.004$) and CTL (218.68 ± 75.30 vs. 261.26 ± 102.05 μmol/L, $p = 0.022$). However, there was no statistic difference in UA level between female NMO and female MS ($p = 0.808$) or female ON ($p = 0.884$). In male subgroups, no difference was found in serum UA level between NMO and CTL ($p = 0.277$), ON ($p = 0.149$) or CI ($p = 0.451$). However, serum UA in male NMO was marginally higher than in male MS (331.90 ± 89.20 vs. 285.56 ± 130.97 μmol/L, $p = 0.031$) Fig. 2.

In NMO, the UA level was not higher in patients with short disease duration (≤1 year) than in longer disease duration (>1 year) ($p = 0.215$) (Table 4). Patients with moderate or severe disability (EDSS > 3.5) had lower serum UA levels compared to those with mild disability (EDSS ≤ 3.5), but the difference was not significant ($p = 0.103$) (Table 4). However, patients with disease activity demonstrated on MRI had higher serum UA level than patients with no activity on MRI, but the difference did not reach statistical significance ($p = 0.263$) (Table 4).

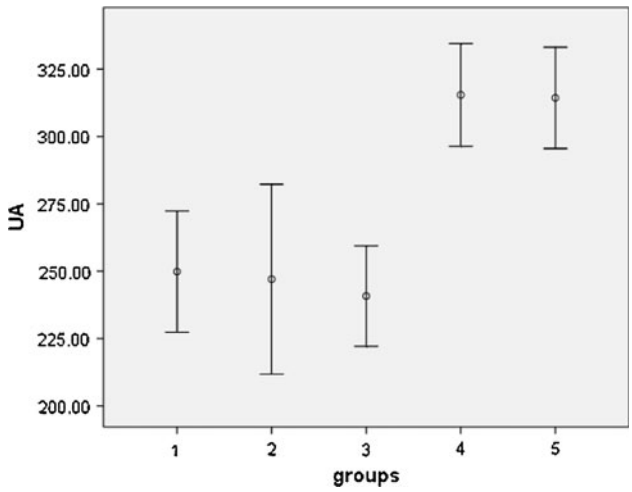

Fig. 1 Distribution of UA level in serum samples of patients and healthy controls. *1* neuromyelitis optica, *2* optic neuritis, *3* multiple sclerosis, *4* cerebral infarction, *5* healthy controls

Table 2 Serum uric acid levels in patients and healthy controls

Patients	Mean ± SD (μmol/L)	Range (μmol/L)	*p**
Neuromyelitis optica	249.89 ± 93.74	60.8–564.2	
Optic neuritis	247.05 ± 97.63	105.0–481.3	0.858
Multiple sclerosis	240.79 ± 106.16	40.2–623.4	0.496
Cerebral infarction	315.42 ± 85.57	86.5–533	0.004
Healthy controls	314.33 ± 102.05	59.6–536.4	0.001

* NMO versus each different group

Table 3 Serum UA levels in male and female patients and healthy controls

Patients	Male (μmol/L)	Female (μmol/L)	*p*1*	*p*2†	*p*3‡
Neuromyelitis optica	31.90 ± 89.20	218.68 ± 75.30	0.001		
Optic neuritis	291.62 ± 101.74	220.32 ± 86.90	0.033	0.149	0.884
Multiple sclerosis	285.56 ± 130.97	213.56 ± 76.71	0.000	0.031	0.808
Cerebral infarction	330.05 ± 91.36	293.48 ± 71.94	0.049	0.451	0.004
Healthy control group	368.53 ± 92.05	261.26 ± 102.05	0.001	0.277	0.022

* Male versus female in each group

† Male patients with optic neuritis, multiple sclerosis, cerebral infarction or healthy control group versus male patients with neuromyelitis optica

‡ Female patients with optic neuritis, multiple sclerosis, cerebral infarction or healthy control group versus female patients with neuromyelitis optica

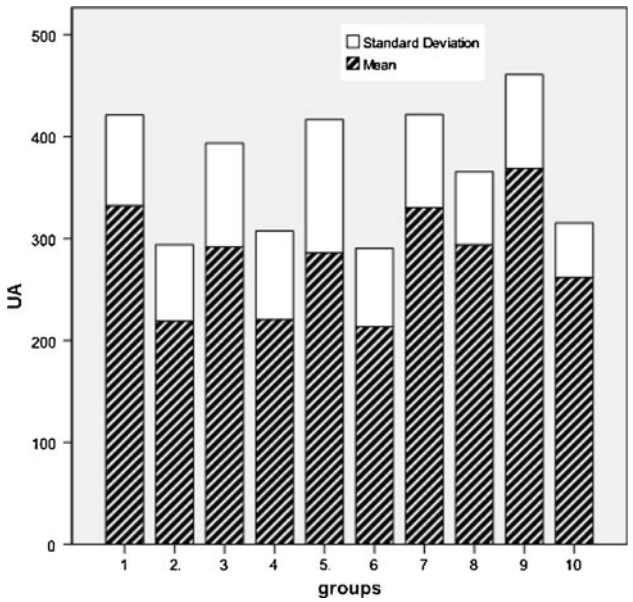

Fig. 2 Serum UA level of men and women in each group. *1* neuromyelitis optica, male, *2* neuromyelitis optica, female, *3* optic neuritis, male, *4* optic neuritis, female, *5* multiple sclerosis, male, *6* multiple sclerosis, female, *7* cerebral infarction, male, *8* cerebral infarction, female, *9* healthy controls, male, *10* healthy controls, female

Table 4 Serum UA levels in patients with neuromyelitis optica

Variables	Mean ± SD (μmol/L)	Range (μmol/L)	*p**
Disease duration			
≤1years, $n = 40$	269.68 ± 80.84	173.2–564.2	
>1years, $n = 29$	222.51 ± 104.42	60.8–320.3	0.215
MRI activity			
Active, $n = 39$	270.69 ± 101.72	60.8–564.2	
Inactive, $n = 19$	238.45 ± 79.17	81.5–385.3	0.263
EDSS			
≤3.5, $n = 33$	272.45 ± 74.41	126.5–419.1	
>3.5, $n = 36$	229.15 ± 105.30	60.8–564.2	0.103
Sex			
Female, $n = 50$	218.68 ± 75.30	60.8–364.5	
Male, $n = 19$	331.90 ± 89.20	173.2–564.2	0.000

Correlation of serum UA levels with disease duration, MRI activity, disability and sex

MRI magnetic resonance imaging, *EDSS* Expanded Disability Status Scale

* Compared UA levels between two subgroup of NMO

Discussion

We found that UA in patients with NMO was lower than that in CI and CTL. However, there was no significant difference between NMO and MS or ON. These results were also observed when the female cohort was investigated separately. A high proportion of NMO patients also showed UA level below the lower limit of the normal range in our cohort. Since a low UA level has been reported in MS and ON [8–10], our results suggested it also happened in NMO. To our knowledge, this was the first report of an association between UA and NMO.

Neuromyelitis optica is a disease with a heterogeneous pathology which involves variations in the representation of T cells, B cells or macrophages in relation to the variable levels of oligodendrocyte programmed cell death [17]. The role of oxidative stress (OS) in NMO has not been fully studied. It is speculative that free radical oxygen chemistry may contribute to the pathogenesis in this condition [18]. Pentón-Rol et al. [19] found almost undetectable levels of TNF-α, a decreased production of IL-10 and a significant up-regulation of every OS biomarker in NMO. Her results suggested that a TNF-α and IL-10 down-regulation and marked OS existed in NMO. Reactive oxygen and nitrogen species play a major role in the inflammation and demyelination of MS [4]. OS can potentially cause cell death by damaging the lipids, proteins and nucleic acids of cells and mitochondria. Oligodendrocytes are more sensitive to OS than other cells in CNS [20]. As a strong scavenger of PN, UA treatment was shown to be able to suppress the inflammatory cascade, decrease blood–brain barrier permeability, and diminish CNS tissue damage and neuronal death in animal models of MS [3]. In contrast, increased serum UA might help to prevent the secondary cellular damage of spinal-cord injury and promote the recovery of motor function [21]. The protective role of UA has already been proven in a rat model of pneumococcal meningitis [22].

Previous studies in MS have reported a moderately low UA in remission stage and much lower UA in the relapsing stage [23, 24]. UA has been considered as a surrogate marker of MS activity. Interestingly, in this study, patients with NMO also showed reduced serum UA. Nevertheless, there were still some uncertainties about whether low serum UA was a cause or a consequence of NMO activity. Further studies are warranted to clarify the underlying mechanisms of UA in NMO.

Serum UA level has been shown to be dependent on both age and gender. In this study, we further divided each group into female and male subgroups. We also found that UA level in female MS was significantly lower than in female patients in all groups, which was consistent with previous studies in MS [8, 23, 25]. Although several studies have attempted to explore why female MS patients tend to have lower UA level [8, 23, 25], there was not any consistent explanation. In this study, serum UA level in female NMO was also significantly lower compared to that in female CI and CTL. In addition, there was no significant difference of serum UA level between female NMO and

MS or ON. In male subgroups, serum UA level in male NMO was not significantly lower compared with male CTL. There was no significant difference between male NMO and ON or CI. However, serum UA level in male NMO was marginally higher compared to male MS. As the number [19] of male NMO was relatively small in our cohort, a further study of more male patients was necessary to confirm our findings.

Previous studies reported that UA level was not correlated with disease activity, duration, disability or disease course in MS [26, 27]. In the present study, UA level in patients with NMO was not correlated with disease activity on MRI, disability or duration of disease, which was similar to the reports in MS. The absence of any correlation between UA levels and MRI activity in this study suggested that the role of UA in disease activity was far from clear. It was also uncertain whether the low UA level in patients with MS was a cause or a consequence of the disease activity [9].

To conclude, this was the first study showing that NMO patients had low serum UA level. Although there were some uncertainties about whether low serum UA level was a cause or a consequence of the disease, it was possible that NMO patients with low serum UA level were unable to prevent free radical toxicity which leads to the development of inflammation and destruction of tissues; it is also possible that the inflammation occurring in NMO leads to the consumption of UA by scavenging the excessively produced free radicals, and a lower UA level in consequence. Since no clinical trials dedicated to treat NMO in acute stage or in preventing relapses have been conducted [27], administration of UA or its precursor should be considered as a replacement therapy to patients with reduced UA serum level.

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