

Serum Uric Acid Levels in Patients with Relapsing-Remitting Multiple Sclerosis



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ABSTRACT

Aim: Multiple sclerosis (MS) is an inflammatory demyelinating disease with unknown origin. Several studies suggest lower levels of serum uric acid (UA), an endogenous antioxidant, in MS patients.

Methods: In this study, we aimed to investigate serum UA levels in relapsing-remitting (RR) MS. In addition we compared serum UA levels by means of clinical activity, expanded disability status scale (EDSS) and disease duration.

Results: In the present study, mean serum UA levels were lower in RRMS and relapse patients with MS than in the other neurological diseases (OND) group, but the difference did not reach significance level. UA levels did not correlate with clinical activity, EDSS score and disease duration either in relapse or remitting or both of them.

Conclusion: In conclusion, this study suggests serum uric acid levels may affect neither pathogenesis of MS nor activity of disease. Further studies are needed to clarify the role of uric acid in MS patients.

Key words: Uric Acid, Activity of Multiple Sclerosis, Endogenous Antioxidant, Pathogenesis.

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INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating disease with a broad clinical variability. The main disease courses are relapsing-remitting, secondary progressive and primary progressive MS. Relapsing-remitting MS (RRMS) is characterized by clearly defined exacerbations followed by periods of stability (1). Uric acid (UA), which is the final product of purine nucleoside metabolism, is a strong peroxynitrite scavenger (2). In MS, plaque areas in the brain associated with peroxynitrite-mediated damage (3). Several studies demonstrated the role of increased free radical production and/or decreased antioxidant defense in MS patients as a causal factor of disease (4). Peroxynitrite can be generated in the Central Nervous System (CNS) in different ways (5). Peroxynitrite (ONOO), the reaction product of NO and superoxide, is a potent oxidant (6), which can be formed in an inflammatory response and can cause a variety of toxic effects. This product may be responsible for a significant proportion of the damage attributed to NO and therefore may be an important factor in the generation of CNS lesions. Several studies suggest lower levels of serum UA in MS patients (7-9). In the other hand, there were several reports concerning no correlation with lower levels of serum UA, in the literature (10). UA has a therapeutic effect in an animal model disease of MS. It suggests UA may scavenge peroxynitrite (3,11).

In this study, we aimed to investigate serum UA levels and its association with clinical activity of disease in RRMS.

MATERIAL and METHODS

The study included 51 (37 remitting; 14 relapse) patients with RRMS diagnosed on the basis of McDonald's criteria (12) and 14 healthy control subjects. All patients were subjected to serial clinical examinations, magnetic resonance investigations and neurophysiological and neuropsychological assessments. Disability was measured using the Kurtzke Expanded Disability Status Score in patients (13). Diagnosis was confirmed by positive conventional magnetic resonance imaging of the brain findings according to the criteria of Paty (14). We determined data concerning demographic variables as age and sex, and clinical variables as age of onset, disease course, disease duration. All patients received either subcutaneous injections of 8 million units of Interferon β 1b at every 2 days (Betaferon, Schering, Berlin, Germany), or intramuscular injections of 30 μ g of Interferon β 1a once a

week (Avonex, Biogen, Cambridge, USA) or subcutaneous injections of 22 μ g of Interferon β 1a three times a week (Rebif, Serona, Geneva, Switzerland).

Exclusion criteria for MS and control subjects were treatment with acetylsalicylic acid, thiazide diuretics, steroids, ibuprofen and other drugs that could increase or reduce UA levels as well as subjects with diabetes mellitus or renal failure (15,16).

Peripheral venous blood samples were collected, serum was separated and stored at -70°C until assayed. UA levels were measured by using a quantitative enzymatic assay according to the manufacturer's protocol by Hitachi 717 autoanalyzer (Boehringer Mannheim, Germany).

Statistical Analysis

UA levels are expressed as mean \pm SD. The significance of differences between groups of patients was assessed using the Kruskal-Wallis test and Mann-Whitney U-test. Associations between variables were tested using Spearman's rank correlation test. A p value < 0.05 was considered significant.

RESULTS

Baseline characteristics and serum UA levels of patients with RRMS and control subjects were shown in table. Mean serum UA levels were lower in the RRMS and relapse patients with MS than in the controls, but the difference did not reach significance level. UA levels did not correlate with clinical activity, EDSS score and disease duration either in relapse or remitting or both of them.

DISCUSSION

MS is an inflammatory, principally demyelinating disease of the central nervous system with suspected autoimmune pathogenesis. Both genetic and environmental factors play a role in its etiology (1).

The changes observed in the blood of MS patients indicate enhanced generation of reactive oxygen species. Reactive oxygen species are thought to play a major role in destruction of the myelin sheath. Increased lipid peroxidation, which has been observed in MS (17), and the oxidation of DNA which may lead to DNA breakage or mutations play significant roles in peroxynitrite-mediated toxicity (18). Furthermore, several findings suggest a potential role of peroxynitrite in the pathogenesis of demyelinating lesions (5). It has been speculated that UA is an important antioxidant in humans (19) protecting oxidative stress in

Table 1. Baseline characteristics and serum UA levels of patients with RRMS and OND groups.

	Remitting (n: 37)	Relapse (n: 14)	Control group (n: 14)
Age (year)	32.4 ± 9.4	31 ± 0.7	35.5 ± 10
Disease duration (year)	4.6 ± 3	4.3 ± 3	–
EDSS score	3.0 ± 1.5	3.6 ± 1.6	–
UA (mg/dL)	3.9 ± 1.3	3.5 ± 1.8	4.1 ± 1.4 3.9

EDSS: Expanded Disability Status Scale

Characteristics were given as mean ± SD. Differences between groups were performed using the Mann-Whitney-Rank Sum test and Kruskal-Wallis test.

the central nervous system (20). The balance between the plasma concentrations of lipid peroxides and blood nonenzymatic antioxidants (GSH, α -tocopherol, retinol, plasma SH groups, and uric acid) in relation to the clinical state of RRMS patients (n=25) were examined in a previous study (21). In mentioned study, there were no significance differences in the exacerbation, remission, remission + interferon β and control groups by means of serum uric acid levels. UA, which is the final product of purine nucleoside metabolism, is a strong peroxynitrite scavenger (2).

In experimental allergic encephalomyelitis, a rodent model for MS, administration of UA, was found to have strong therapeutic effects (3). Several studies showed lower levels of serum uric acid in MS patients (7,11,22,23,25), and also Mattle et al. (25) reported that uric acid levels were decreased in MS patients when compared to control subjects along with in patients with relapse were lower than in patients in remission. Serum UA levels were lower in the mono- and dizygotic twins with MS than in the healthy twin (7). In this study, mean serum UA levels were lower in the RRMS than in the controls, but the difference did not reach significance level. The limitation of our study is the presence of restricted patient numbers. These data are in accordance with the results of Drulovic et al (10). In Drulovic et al's study (10) mean serum UA levels were lower borderline ($p=0.046$) in relapse patients than remitting patients. In a previous study, serum UA levels did not significantly correlate with clinical activity EDSS score and disease duration (9). Our results are in accordance with the results of above-mentioned study. As a similar our findings, Drulovic et al's (10) and M. Rentzos (11) revealed that there was no correlation between the level of UA and EDSS and disease duration, although M. Rentzos showed uric acid levels

were decreased in MS patients compared with controls. Also, in all reports, the gender matched were performed by authors. Some of them demonstrated that the level of serum UA was lower in female MS patients than male patients (7,10). There were some speculations for these results. One of them is that these findings may more contribute to the mechanism of MS in female patients than in male subjects (26). Adversely, we did not observed the differences of gender in terms of the level of serum UA.

In the present study, all RRMS patients received Interferon- β . Serum UA levels were not affected by Interferon- β treatment for MS (27) and also RRMS (11,28).

In conclusion in our study serum uric acid levels may affect neither pathogenesis of MS nor activity of disease. Further studies are needed to clarify the role of uric acid in MS patients.

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