Serum uric acid levels in patients with myasthenia gravis are inversely correlated with disability

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Uric acid (UA), the final product of purine metabolism, has been reported to be reduced in patients with various neurological disorders and is considered to be a possible indicator for monitoring the disability and progression of multiple sclerosis. However, it remains unclear whether there is a close relationship between UA and myasthenia gravis (MG), or whether UA is primarily deficient or secondarily reduced because of its peroxynitrite scavenging activity. We investigated the correlation between serum UA levels and the clinical characteristics of MG. We assessed 338 serum UA levels obtained in 135 patients with MG, 47 patients with multiple sclerosis, and 156 healthy controls. In addition, we compared serum UA levels when MG patients were stratified according to disease activity and classifications performed by the Myasthenia Gravis Foundation of America, age of onset, duration, and thymus histology (by means of MRI or computed tomography). MG patients had significantly lower serum UA levels than the controls ($P<0.001$). Moreover, UA levels in patients with MG were inversely correlated with disease activity and disease progression ($P=0.013$). However, UA levels did not correlate significantly with disease duration, age of onset, and thymus histology. Our findings suggest that serum level of UA was reduced in patients with MG and serum UA might be considered a surrogate biomarker of MG disability and progression. NeuroReport 2016, 27:301–305 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Myasthenia gravis (MG), caused by autoantibodies against the acetylcholine receptor (AChR) on the postsynaptic membrane at the neuromuscular junction, is an acquired autoimmune disease characterized by a defective transmission of nerve impulses to muscles [1]. Accumulating data have implicated oxidative stress in the immunopathogenesis of neuromuscular diseases [2,3].

As the final product of the common pathway of purine metabolism, uric acid (UA) is a naturally occurring antioxidant, with metal-chelating properties [4]. Previous studies have reported that UA can scavenge nitrogen radicals and superoxide, thus helping to block the generation of the strong oxidant peroxynitrite [5]. Peroxynitrite exerts toxic effects and irreversibly jeopardizes cellular metabolism and cell structures, including lipids, carbohydrates, protein, and DNAs [6]. Several studies have identified a therapeutic role of UA in experimental allergic encephalomyelitis and a beneficial function for increasing serum UA levels in multiple sclerosis (MS) patients [7,8]. Furthermore, UA might be a surrogate marker for monitoring MS activity [9].

Therefore, the aim of this study was to investigate whether the serum UA levels were decreased in MG patients and whether the decrease was associated with disease disability and progression.

Patients and methods

Serum samples were collected from 338 individuals: 135 patients with MG, 47 patients with MS, and 156 healthy controls (CTL). Venous blood was drawn from an antecubital vein in the morning after an overnight fast to measure the concentration of serum UA using a Clinical Analyzer Beckman Coulter AU5831 (Beckman Coulter, Brea, California, USA). In our hospital, the normal range of serum UA values is 208–428 μM for men and 155–357 μM for women. Simultaneously, concentrations of glutamate–pyruvate transaminase (normal range: 9–50 μM for men, 7–40 μM for women), glutamic–oxaloacetic transaminase (normal range: 15–40 μM, 13–35 μM for women), blood fasting sugar, and blood urea nitrogen were also measured using an enzymatic method on the same analyzer.

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The basic demographic and clinical characteristics of patients with MG, patients with MS, and healthy controls are shown in Table 1. In total, 338 individuals provided samples. These included 135 MG patients (57 men, 78 women), 47 MS patients (13 men, 34 women), and 156 controls (CTL, 69 men, 87 women), who did not differ significantly in age (MG 41.6 ± 15.8, MS 41.5 ± 10.5, CTL 42.9 ± 14.3; P = 0.684).

In the present study, the mean serum UA level in all participants was 304.9 ± μM. The serum UA level was significantly lower in the MG patients than in the healthy controls (283 ± 90 vs. 335 ± 84 μM; P < 0.001). However, no difference was found between MG and MS (283 ± 90 vs. 257 ± 85 μM; P = 0.072) (Fig. 1). Previous evidence has shown that serum UA levels are significantly lower in women than in men [12]. Accordingly, we divided each cohort into men and women to eliminate the possibility that the differences that we observed were simply because of the different numbers of men and women in the disease groups. Interestingly, in all groups, the serum UA level in women was significantly lower than that in men (P < 0.001) (Table 2 and Fig. 2). Compared with CTL patients, MG patients had lower serum UA level, whether male or female. However, there was no statistical difference in UA levels between patients with MG and MS, whether in male or in female subgroups (P = 0.641 and 0.204, respectively) (Table 2 and Fig. 2).

The correlations between UA levels in MG patients, with their disease duration, age of onset, MGFA clinical classification, and thymus histology, are presented in Table 3. In MG, the UA level was not lower in patients with late-onset MG (age at onset ≥ 50 years) than early-
onset MG (age at onset < 50 years) (P = 0.664) (Table 3).
There was no significant difference (P = 0.261) in UA levels between patients with longer disease duration (> 1 year) and those with short disease duration (≤ 1 year), although the former was somewhat lower than the latter (Table 3). The serum UA level was not lower in patients with thymoma shown on MRI or computed tomography than in patients without thymoma (P = 0.867). However, we found that the relative decrease in the mean serum UA level of the patients with MG correlated inversely with the degree of disease progression, as expressed by the MGFA clinical classification (Table 3 and Fig. 3). On grouping MGFA IIa, IIIa, and IVa categories (absence of bulbar involvement) and comparing them with IIb, IIIb, and IVb categories (presence of bulbar involvement), no significant difference was observed between bulbar independent and involved bulbar MG patient groups (Table 3).

**Discussion**

MG is a severe autoimmune disease characterized by its tendency to selectively affect AChR of the postsynaptic membrane, which is associated with B and T cell activation [13]. The role of oxidative stress in MG has not been fully studied. Reactive oxygen species play a role in injuring the body’s cells and tissues through multiple pathways, including direct damage to the biological structures, such as cell membrane, genetic material, and enzymes, and indirectly stimulating the expression of genes associated with apoptosis. Furthermore, accumulating evidence has shown that oxidative stress contributes toward the pathogenesis in inflammatory and autoimmune-mediated tissue destruction [14]. Skeletal muscle is strongly dependent on oxidative metabolism,
and corresponding antioxidant protection mechanisms are present. Venkatesham et al. [3] have shown that reactive oxygen species might contribute toward damage to the AChR. Moreover, Krishnaswamy and Cooper [15] has suggested that the highly conserved cysteine residues in nicotinic AChRs are the major targets of reactive oxygen species producing receptor dysfunction. Highly conserved cysteine residue, a component of several nicotinic AChRs on neurons, locates near the intracellular mouth of the receptor pore and enables ganglionic transmission and sympathetic reflexes to function normally.

UA, a naturally occurring product of purine metabolism, is an important natural antioxidant that could scavenge superoxides and reduce oxidative stress [16]. Numerous studies have shown that there is a reduced serum UA level in inflammatory and autoimmune diseases [17–19]. Previous studies in MS showed that UA may be a surrogate marker of MS activity and it is one of the antioxidants evaluated for their effect on MS disease progression [20]. Moreover, UA treatment has been proven to prevent inflammation and destruction of central nervous tissue and ameliorate established disease in the animal models of MS [21].

In this study, MG patients presented significantly lower serum UA than healthy controls. However, the difference in serum UA between MG patients and MS patients was not significant. Furthermore, similar results were also observed when the female and male cohorts were investigated separately. A relatively high proportion of patients with MG, in our hospital, had serum UA levels below the lower limit of the normal range, which was similar to the previous report [22]. However, the correlation between the serum UA and the clinical characteristics of MG was not investigated in the previous study. To better clarify the underlying mechanisms of antioxidant status in MG, patients were divided into five subgroups according to the MGFA clinical classification. Patients with clinically active disease had significantly lower UA levels than those with clinically inactive disease. However, comparison of UA levels in patients stratified according to MG disease duration, age of onset, and thymus histology showed no significant difference. Nevertheless, it was also uncertain whether a low concentration of UA was a cause or a consequence of MG progression and activity. Further studies are necessary to clarify the role of UA and its underlying mechanisms in patients with MG. Nonetheless, patients with MG were unable to protect neuromuscular junction against oxidative stress with low antioxidant status.

**Conclusion**

Our findings of a significant inverse correlation between serum UA level and disease activity and disability, as assessed by the MGFA clinical classification, indicate that serum UA might serve as a possible biomarker of disease disability in MG. To our knowledge, the present study is the first description of an inverse correlation of serum UA level with MG disability as assessed by the MGFA clinical classification. Confirmation of these conclusions with a much larger sample will be an important next step.

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**Conflicts of interest**

There are no conflicts of interest.

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