Assessment of Serum Uric Acid Levels in Multiple Sclerosis during Disease-Modifying Treatment

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Abstract

Objective: Uric acid is a potent endogenous antioxidant and scavenger of peroxynitrite (PN), which hypothesized to be involved in the pathogenesis of multiple sclerosis (MS). Some studies reported lower levels of UA in MS patients compared with controls, whereas other studies found no difference. The main purpose of this analysis was to verify the hypothesis on lower serum levels of UA in MS patients compared with controls.

Materials and methods: We examined 80 patients with clinically defined MS, according to the McDonald's criteria and 53 patients of controls group (non-inflammatory neurological diseases, excluding vascular disorders). Uric acid concentration was determined by using a commercially available enzymatic colorimetric assay according to the manufacturer's instructions.

Results: Serum UA levels of MS patients were significantly lower (4.2 ± 1.1 mg/dl) when compared with control group (4.9 ± 1.4 mg/dl, P=0.0092). Correlation between MS duration and serum UA concentration did not reach statistical significance, however the tendency showing that patients who are suffering from this disorder for a longer time have lower serum UA concentration was observed. Moreover, we found a statistically significant correlation between disease duration and UA concentration in a subgroup of patient who did not have a history of mitoxantrone intake (P<0.0321).

Conclusion: Although we do not know exactly whether and how uric acid is involved in MS pathogenesis, data suggest that UA concentration is lower in MS patients than in control group. It seems that low uric acid levels indicate patients with a higher risk of disease progression. Whether or not UA concentration can be useful as a biomarker in MS requires further study.

Keywords: Uric acid; Multiple sclerosis; Immunomodulatory therapy; Disease-modifying treatment; Immunosuppression; Antioxidant

Introduction

Altered serum uric acid (UA) concentration, both above and below normal levels is a known risk factor of many diseases. High serum UA level causes gout and is a risk factor for hypertension, cardiovascular and renal diseases. Reduced UA concentration was reported in multiple sclerosis, Parkinson's disease, Alzheimer's disease and optic neuritis [1,2]. Some studies suggest that UA has two functions: injurious and neuroprotective [3]. Experimental studies have shown that hyperuricemia is associated with endothelial dysfunction, local oxidant generation, elevated circulating levels of systemic inflammatory mediators such as monocyte chemotactant protein-1, NF-kB, interleukin-1β, interleukin-6 and tumor necrosis factor-α and vascular smooth muscle proliferation [4,5]. Uric acid, product of purine metabolism, is a potent endogenous antioxidant and scavenger of peroxynitrite (PN). PN was hypothesized to be involved in the pathogenesis of multiple sclerosis (MS) through its various neurotoxic effects. UA and UA precursors, such as inosine, reduces inflammatory and demyelination in experimental allergic encephalomyelitis [6,7].

Some studies reported lower levels of UA in MS patients compared with controls, whereas other studies found no difference. Positive therapeutic effect was reported using inosine to treat MS patients as a method of raising the serum UA concentration [8]. The literature reports inconsistent results on the relationship between UA level and disease activity [9,3,10,11]. A significant decrease in uric acid in 2 year follow-up in patients with relapsing-remitting multiple sclerosis was found. They suggest this is due to the progressive loss of antioxidant reserves.

The main purpose of this analysis was to verify the hypothesis on lower serum levels of UA in MS patients compared with controls. In addition, we aimed to study the correlations between UA concentration and MS clinical parameters as well as immunomodulatory and immunosuppressive therapies.

Patients and Methods

We examined 80 patients with clinically defined MS, according to the McDonald's criteria. There were 54 females and 26 males; mean age
of 38.7 ± 10 years; mean disease duration of 9.3 ± 7.0 years; mean EDSS score of 3.4 ± 1.7. In 41 patients MS course was relapsing-remitting, in 32 progressive relapsing, in 7 secondary progressive. Twenty six patients were treated with mitoxantrone, the other 31 were taking IFN-β, 7 subjects were administered with glatiramer acetate, 1 with natalizumab and 1 with fingolimod. Controls group consisted of 53 patients with other non-inflammatory neurological diseases (excluding vascular disorders): 23 females and 30 males, mean age of 43.6 ± 11 years.

Uric acid concentration was determined by using a commercially available enzymatic colorimetric assay according to the manufacturer’s instructions. In our hospital the normal range of UA values is 2.8-7.0 mg/dl.

Statistical analysis of data was performed using the SAS (SAS Institute). Statistical significance was considered at P<0.05. The following descriptive statistics: median, mean, standard deviation (SD), minimum and maximum values in the total study population were calculated for each quantitative variable. Continuous variables were assessed by Wilcoxon two-sample test. Spearman and Pearson Correlation Coefficients were used to measure the statistical relationship between two continuous variables.

**Results**

In our study serum UA levels of MS patients were significantly lower (4.2 ± 1.1 mg/dl) when compared with control group (4.9 ± 1.4 mg/dl, P=0.0092). However, only four MS patients (5% of all patients) had UA levels below the lower limit of the normal values. There was no correlation between the UA levels and following parameters: patient’s age, MS duration, EDSS, ΔEDSS, number of relapses per two years and MS course: RRMS, PRMS, SPMS. Correlation between MS duration and serum UA concentration did not reach statistical significance (P pearson<0.1468, R pearson=-0.1752; P spearman<0.0924, R spearman=-0.2017), however the tendency showing that patients who are suffering from this disorder for a longer time have lower serum UA concentration was observed. Moreover, we found a statistically significant correlation between disease duration and UA concentration in a subgroup of patients who did not have a history of mitoxantrone intake (P pearson<0.0321, R pearson=-0.32). Table 1 shows correlations between UA levels and all parameters.

| Correlations between uric acid levels and... | Statistical significance | P value | R value |
|--------------------------------------------|--------------------------|---------|---------|
| Age                                        | NS                       | 0.9896  | 0.014   |
| The number of relapses in the last 2 years | NS                       | 0.4968  | -0.0775 |
| EDSS                                       | NS                       | 0.916   | 0.0121  |
| DEDSS                                      | NS                       | 0.0528  | -0.2201 |
| MS duration                                | NS                       | 0.0763  | -0.2131 |
| MS duration in patient treated with mitoxantrone | NS          | 0.4754  | 0.1495  |
| MS duration in patients not treated with mitoxantrone | S                 | 0.0321  | -0.32   |

Table 1: Correlations between uric acid concentration and variable parameters.

EDSS: Expanded Disability Status Scale; DEDSS: Delta-Expanded Disability Status Scale–EDSS progression in the last 2 years; NS: Not Significant; S: Significant

**Discussion**

In our study we observed lower levels of UA in MS patients than in control group. Several studies reported UA concentration in MS patients. Few found serum UA levels to be significantly lower in MS patients than in controls [3,7,9-12], while the others observed no such difference [13]. Massa et al. [14] carried out the study suggesting that serum UA is not a strong predictor of MS risk. The authors state that the lack of association is consistent with the interpretation that the lower UA levels among multiple sclerosis cases are a consequence rather than a cause of the disease. Guerrero et al. [15] show an inverse correlation of serum UA levels with disability as assessed by EDSS score. A recently published article has shown a correlation between uric acid levels and the occurrence of benign multiple sclerosis. Increased concentration of uric acid was associated with the presence of benign MS [16].

In some studies correlation between UA concentration and disease activity [3,10,17,18] was observed. On the other hand, other studies did not suggest this correlation [9,11,19]. Our findings are partially consistent with these latter reports. We observed lower UA concentration, but no significant correlation with disease activity and disability. Interesting is our observation that UA concentration correlates with MS duration in patients who were not treated with mitoxantrone (MTX). The MTX treatment is immunosuppressive therapy, which markedly reduces MS activity and progression. The impact of the immunomodulatory therapies such as with interferon beta or glatiramer acetate on inflammation is less effective.

Decreased uric acid levels are one of the indications of an exhausting antioxidant reserve and may involve the risk of MS progression. Low levels of uric acid would indicate patients who are most at risk for disease progression and who require more intensive treatment. In order to confirm this hypothesis, it is necessary to conduct a study in a larger group of patients, taking into account the various MS therapies currently available.

**Conclusion**

Although we do not know exactly whether and how uric acid is involved in MS pathogenesis, data suggest that UA concentration is
lower in MS patients than in control group. It seems that low uric acid levels indicate patients with a higher risk of disease progression. Whether or not UA concentration can be useful as a biomarker in MS requires further study.

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