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BRIEF COMMUNICATION

Serum uric acid levels in multiple sclerosis patients inversely correlate with disability

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Abstract Uric acid (UA) is an endogenous antioxidant. Some studies have described that multiple sclerosis (MS) patients have lower serum UA levels than controls, although it has not been established whether UA is primarily deficient, or secondarily reduced due to its scavenging activity. UA has also been proposed as an indicator of disease activity. We, retrospectively, reviewed 478 serum UA levels obtained in 94 MS patients. Ninety samples were collected during a relapse. Correlation between UA levels obtained during a relapse or in a relapse-free period, and comparison between UA and expanded disability status scale (EDSS) score was tested using a two-tailed Student's *t* test and Spearman correlation coefficients test. UA levels were significantly lower when measured during a relapse (n 90) than in a remission period (n 368) (r −0.16, p 0.003) UA levels measured outside a relapse inversely correlated with EDSS score (r −0.15, p 0.001). Lower uric acid levels in MS patients are associated with clinical relapse. This is the first description of an inverse correlation of serum UA levels with disability as assessed by EDSS score.

Keywords Uric acid · Multiple sclerosis · Disability

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Introduction

Uric acid (UA), the end product of purine metabolism in humans, is an endogenous antioxidant acting as a natural peroxynitrite scavenger [1]. Peroxynitrite, product of free radicals nitric oxide and superoxide, exerts a toxic effect on neurons, axons, and glia cells, and contributes to demyelination, oligodendrocyte destruction, and axonal damage in multiple sclerosis (MS) [2].

Since in 1998, it was found that gout patients rarely, if ever, develop MS it has been postulated that high levels of uric acid could reduce risk, or favourably influence MS progression. Anyway, it has not been established whether UA is primarily deficient or secondarily reduced due to its scavenging activity [3].

Regarding its influence on disease activity, some authors have shown that UA levels are lower during clinical or magnetic resonance imaging (MRI) activity than during MS remission [4]. Previous studies have only found a non significant trend toward an inverse correlation of serum UA concentration with disability [5].

Materials and methods

We, retrospectively, reviewed medical records of 94 patients followed in our neurology unit throughout a year due to a clinically definite MS diagnosed according to Poser's criteria.

We collected data concerning demographic and clinical variables such as age of onset, disease course, disease duration and Expanded Disability Status Scale (EDSS) score.

We considered 478 serum uric acid (UA) determinations previously obtained in these patients with the uricase PAP

method. Twenty of these values were carried out before clinical disease onset, and 90 were obtained during a relapse, just before steroids treatment.

The 368 remaining determinations corresponded to an attack-free period with no relapse during previous 3 months. In all cases, EDSS score at the moment of blood extraction was estimated. 200 determinations of UA levels were obtained, while patients were receiving treatment with interferon beta, while when 168 samples were collected patients received no disease modifier treatment.

Statistical analysis was performed with SPSS 12.0 software. Level of significance was established at 5%. We compared it with a two-tailed Student's *t* test and Spearman correlation coefficients test.

1. UA levels obtained during relapse or relapse free period.
2. UA levels determined in a relapse free period with or without inmunomodulatory treatment.
3. UA levels and EDSS score measured outside relapses.

When appropriate, *t* test for paired samples was applied. Values are presented as mean ± standard deviation (SD). Univariate associations significant were entered stepwise into multivariate logistic models.

Results

We reviewed 94 patients (73 female/21 male, ratio 3.47). Clinical subtype distribution was as follows: 73 (77.6%) relapsing remitting MS, 12 (12.7%) Secondary Progressive MS and 9 (9.7%) primary progressive MS. Demographic and clinical characteristics are shown in Table 1.

UA levels were significantly lower when measured during a relapse (*n* 90) than in a remission period (*n* 368) (*r* −0.16, *p* 0.003) (Table 2). There was no correlation between serum UA levels and using of inmunomodulatory treatment. (Table 3). We found no difference in UA levels comparing relapsing remitting and progressive MS patients.

Table 1 Demographic and clinical characteristics of 94 multiple sclerosis patients

	Mean (median)	SD	Range
Age (years)	41.1	11.6	13–66
Age of onset (years)	31.6	10.6	9–51
Duration of disease (years)	9.6	7.4	0.5–31
EDSS	3.1	2	0–9
Progression index	0.6	1.5	0–15

SD standard deviation

Median when EDSS or progression index

Table 2 Serum uric acid levels and relapse

	Relapse	*N*	Mean	SD	*p*
Uric acid	No	368	4.11	1.07	0.003
	Yes	90	3.67	1.02	

Table 3 Serum uric acid levels and immunomodulatory treatment

	Treatment	*N*	Mean	SD	*p*
Uric acid	No	168	4.11	1.04	0.08
	Yes	200	4.09	1.12	

Table 4 Logistic regression analysis

Variable	*p*	RR	CI (95%)
Age (years)	0.0001	0.94	0.92–0.97
Sex	0.53		
Duration of disease (years)	<0.0001	0.84	0.79–0.90
Uric acid	0.0012	0.63	0.48–0.83

Influence on presence of relapse

Table 5 Logistic regression analysis

Variable	*p*	RR	CI (95%)
Age (years)	0.092		
Sex	0.65		
Duration of disease (years)	<0.0001	0.28	0.05–0.11
Uric acid	0.001	−0.17	−(0.43–0.13)

Influence on EDSS score

UA levels measured outside a relapse inversely correlated with EDSS score (*r* −0.15, *p* 0.001). We found no correlation between UA levels and the type of inmunomodulatory treatment received when sample was collected (*r* −0.16, *p* 0.1).

A multivariate logistic analysis was added in order to disentangle the independent contribution of each variable considered to the presence of a relapse or to EDSS score. Data are presented in Tables 4, 5.

Discussion

Inflammatory cells in MS and experimental autoimmune encephalomyelitis (EAE) produce oxidizing substances such as nitric oxide and peroxynitrite. These substances exert a toxic effect on neurons and glia cells, and increase blood–brain barrier (BBB) permeability to inflammatory cells [2, 4].

Uric acid is the naturally occurring product of purine metabolism that acts as a peroxynitrite scavenger,

suppressing increased BBB permeability and inhibiting peroxynitrite-mediated reactions implicated in the pathogenesis of MS [1, 6].

Several studies have shown lower uric acid levels in MS [7–9] or in neuromyelitis optica (NMO) [10] patients than in controls. Anyway, whether it represents a primary loss of protection or a secondary deficit consequence of its scavenging activity is still unclear. Other researchers have not found differences among UA levels between MS patients in a phase of clinical inactivity and controls [11, 12, 15], or even, that purine compounds, including UA are elevated in MS patients [13].

Serum uric acid might serve as a marker of disease activity in MS. Some studies have evaluated correlation between UA levels and activity, disability, disease course, or disease duration with conflicting results.

- Karg et al. [8] (25 relapsing remitting MS) showed no correlation between uric acid levels and clinical activity or immunomodulatory treatment.
- Drulovic et al. [5] (240 MS patients) found a significant inverse correlation of serum uric acid levels with female gender, disease activity and duration, and a trend toward an inverse correlation with disability as assessed by EDSS score.
- Sotgiu et al. [14] (124 MS patients) showed lower serum UA levels in patients with active versus inactive disease, but difference was not significant.
- Toncev et al. [4] (63 relapsing remitting MS) found that patients with relapse or gadolinium enhancing lesions on MRI had lower serum UA levels than those in clinical or radiological remission. They did not find correlation between uric acid levels and EDSS score.
- Mostert et al. [7] (30 patients) described no correlation between UA levels and disease course, or use of immunomodulatory treatment.
- Ramsaransung et al. [9] (82 patients) found no significant changes in uric acid levels between benign, secondary progressive, or primary progressive MS.
- Peng et al. [15] data show that UA levels do not correlate with MRI activity, disability or subtype of disease in 112 MS patients.
- Peng et al. [10] described no correlation between UA levels and MRI activity in 69 patients with NMO.

Increase in UA levels has been suggested as one of the possible mechanisms of action of treatments used in MS, such as methylprednisolone [16], interferon beta [17], or glatiramer acetate [17, 18]. Though it has been hypothesized that high levels of UA could be beneficial in MS patients [19], therapy with interferon beta (IFNB) and inosine, a precursor of uric acid, have not provided additional benefit on accumulation of disability compared with IFNB alone [20].

Conclusion

Our results indicate that lower uric acid levels in multiple sclerosis patients are associated with clinical relapse; serum UA might, so, serve as a possible marker of disease activity in MS.

According to our knowledge, this is the first description of an inverse correlation of serum UA levels with disability as assessed by EDSS score. Though significant, the correlation we obtain is weak, and larger series should be studied to confirm it.

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