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Correlation of interleukin-2 and uric acid plasma concentration with multiple sclerosis in Iranian patients

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ABSTRACT

Multiple sclerosis (MS) is an inflammatory and an autoimmune disease which the immune system can play an important role on its pathogenesis. As uric acid (UA) is considered as an endogenous peroxynitrite-scavenger, it may effect on MS. In this study, concentrations of interleukin-2 (IL2) and UA in plasma samples of MS patients were assessed. One hundred Iranian MS patients (mean± SD age of 32.95 ±6.51 years, range of 20-48 years) from medical genetics department of Sarem Women hospital were selected. Besides, one hundred ethnically, age and sex matched healthy individuals (mean± SD age of 29.8±7.8 years, range of 20-50 years) without personal or family backgrounds of autoimmune disorders were enrolled as a control group. IL2 plasma concentration was calculated by Human IL2 kit of eBioscience Company. Plasma level of UA was detected using Uric Acid Assay Kit of Abcam Company. The Plasma concentration of IL2 was significantly higher in MS patients than controls (8.435×10^{-7}). Also plasma concentrations of uric acid were significantly lower in MS group in comparison with control subjects (1.548×10^{-30}). The patients had around 2.2 times lower UA plasma concentration than controls. Our studies suggested that measurement of plasma IL2 and UA concentrations may provide an objective marker of disease in patients with MS. In addition, it seems that studies with larger sample size are required to bring about more authentic results.

Key words: Interleukin-2, uric acid, plasma concentration, Multiple sclerosis

1. INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease which has been an unresolved issue for the researchers of neuroscience as a result of the complexity of its pathophysiology. It has been proved that activation of the immune system against self-myelin antigens is a common part in the development of the disease; however, the cause remains unknown. Since elevations of serum interlukin-2 (IL2) (1-5) levels in multiple sclerosis patients had been explained in earlier studies and the results demonstrated a possible sign of circulating activated T-cells, assays for the assessment of several other cytokines have become available. T lymphocytes expressing IL2 or IL2 receptor had been found in demyelinated plaques in brains of MS patients (6-8). In addition, elevated cytokine levels were evaluated in serum and CSF of patients with different infectious, inflammatory or malignant diseases (9-14). In other initial experimental studies demonstrated that serum IL2 levels might suggest MS disease activities (15). Trotter et al assessed other cytokines to find out whether they are better candidates for measures of disease activity in highly active chronic progressive patients. Finally, they demonstrated that serum IL2 seems to be the best candidate in chronic progressive MS patients (15). The study of different polymorphisms and alleles of IL2 gene and other genes which are involved in immune system are necessary to find out clearly. Various factors and their genes which may effect on autoimmune disease were studied in different population (16-21). It is recommended that nitric oxide (NO) and reactive oxygen species, yielded from infiltrating immune cells and resident glial cells, can lead to the

myelin and oligodendrocyte injury in Multiple Sclerosis (22). When NO and superoxide are created simultaneously, they may come together to produce the powerful and destructive oxidant, peroxynitrite (23). Applying immuno-histo-chemistry, nitro-tyrosine, a biochemical marker for peroxynitrite-mediated injury, was found in the CNS of MS patients. In addition, it has recently been indicated that EAE can be prevented using peroxynitrite-scavengers (24). Studies among different populations indicated that patients with MS have low serum levels of the UA (25-29). Allameh et al. demonstrated that the positive response of antioxidant system to Uric acid (UA) administration in EAE mice was corroborated with improvement of clinical manifestation of the animals (30, 31). UA is considered as a strong, endogenous peroxynitrite-scavenger (23). New studies comparing serum levels of UA in MS patients and in individuals with other neurological disorders indicated that the average serum UA level in RR and SPMS patients was considerably lower than in controls (23). In a prospective follow-up of serum UA levels in RR patient considerably higher UA levels were observed during remission in comparison with the levels observed within relapses (32). High-dose methylprednisolone treatment in MS patients was detected to induce a considerable increase in serum UA levels (33). These findings suggest that elevated UA serum levels are related with reduced CNS inflammation and tissue damage, and may act as an easily detectable cause of disease activity as well as response to treatment. The aim of this study was to assess the plasma IL2 and UA concentration in MS patients in comparison with controls.

2. MATERIALS AND METHODS

2.1. Patients and controls

One hundred Iranian MS patients (mean± SD age of 32.95 ±6.51 years, range of 20-48 years) from medical genetics department of Sarem Women hospital were selected. The MS diagnosis was made according to the McDonald criteria (34). Besides, one hundred ethnically, age and sex matched healthy individuals (mean± SD age of 29.8±7.8 years, range of 20-50 years) without personal or family backgrounds of autoimmune disorders were enrolled as control group. This work was approved by Trbiat modares University ethical committee and all individuals were signed the written informed Consent. Demographic and clinical profiles of MS patients and controls were demonstrated in Table1.

2.2. IL2 and Uric acid assay

Plasma was isolated from peripheral blood samples which collected in EDTA tube. IL2 plasma concentration was calculated by Human IL2 kit of eBioscience company. Plasma level of UA was detected using Uric Acid Assay Kit of abcam company. These kits were applied according their manufacturer's recommendations.

2.3. Statistical analysis

Mean plasma concentration of IL2 and uric acid was calculated. Comparisons between IL2 and uric acid plasma concentration of MS patients and controls were made using the independent t-test. All the analyses were done using SPSS 18v. P value <0.05 was considered as significant. SPSS 18.0 for windows software was applied.

3. RESULTS AND DISCUSSION

The demographic and clinical features of MS patients and controls were demonstrated in Table1. The clinical characteristics revealed that all patients had relapsing-remitting MS, the mean age of onset, duration and EDSS were 32.95 ±6.51, 5.86 ± 5.535, and 3.775 ± 2.226 years, years, respectively (Table 1).

Table 1. Demographic and clinical profiles of MS patients and control group

Variables	MS patients	Control
Female/Male [No. (%)]	59(59%)/41(41%)	60(60%)/40(40%)
Age (mean ± SD, year)	32.95 ±6.51	29.8±7.8
Age Range (years)	20 - 48	20-50
Age at onset (mean ± SD, year)	28.3 ± 4.2	-
Relapsing-Remitting Course [No. (%)]	100 (100%)	-
Duration (mean ± SD, year)	3.86 ± 5.535	-
EDSS[a] (mean ± SD)	3.775 ± 2.226	-

[a] Expanded Disability Status Scale of Kurtzke.

The mean plasma concentration of IL2 and UA in MS patients and controls was shown in Table 2, Table 3.

Table 2. Mean plasma concentration of IL2 in MS patients and controls

	Patient (N=100)	Control (N=100)	P[a]	95% CI
Mean concentration of IL2±SD (ng/ml)	**0.722±0.751**	**0.306±0.283**	**8.435×10^{-7}**	**0.257-0.574**

a: value of independent t-test. N: number of individuals.

Table 3. Mean plasma concentration of UA in MS patients and controls

	Patient (N=100)	Control (N=100)	P[a]	95% CI
Mean concentration of UA±SD (mg/dl)	1.608±0.59	3.537±1.174	1.548×10^{-30}	1.67-2.189

a: value of independent t-test. N: number of individuals

The patient group showed significantly higher IL2 plasma concentration in comparison with controls. Plasma concentration of IL2 was 0.722 and 0.306 ng/ ml in the MS patients and healthy control group, respectively (p: 8.435×10^{-7}). Also Mean plasma concentration of UA in patients and controls was 1.608 and 3.537 mg/ dl, respectively. Their comparisons showed statistical significant decrease in patient group (p: 1.548×10^{-30}). The patients had around 2.2 times lower UA plasma concentration than controls (Table 3). Elevated cytokine levels were evaluated in serum of patients with different infectious, inflammatory or malignant diseases (9-14). In other initial experimental studies demonstrated that serum IL2 levels might suggest MS disease activities. Moreover, it is recommended that reactive oxygen species, yielded from infiltrating immune cells and resident glial cells, can lead to the myelin injury in Multiple Sclerosis (22). Study on EAE mice demonstrated that the positive response of antioxidant system to Uric acid (UA) administration in EAE mice was corroborated with improvement of clinical manifestation of the animals (30, 31). More recent biochemical, molecular and pathological studies advocate an important potential role of neuro-degeneration in multiple sclerosis. The aim of present study was to assess the influence of IL2 and UA plasma concentration on MS disease. Our results indicate that the patient group showed significantly higher IL2 plasma concentration in comparison with controls. This result is similar to the study in UK which indicated concentrations of IL2 were significantly higher in MS compared with control subjects and they suggested that measurement of IL2 concentrations might provide an objective marker of disease activity in MS patients (35). In one study in USA, it was shown that plasma IL2 concentration displayed higher level than controls. Indeed, Plasma IL2 levels among other cytokines IL-Iα, IL-lβ, IL2, IL4, IL6 were the only cytokine level to achieve significance in statistical analyses (15). Our results showed that the patient group showed significantly higher UA plasma concentration in comparison with controls. Consistent with our results, one study on Italy population showed MS patients had significantly lower serum urate levels than controls (36). Rentzos et al. in 2006 reported that in the overall MS group, patients were found to have significantly lower mean serum uric acid levels compared with the inflammatory, the non-inflammatory diseases and control group . Their findings suggest that lower serum UA levels in MS patients may represent a primary, constitutive loss of protection against nitric oxide and the development of CNS inflammation. They also provided support that the earlier increase of UA serum levels might be beneficial in the future treatment of MS (37). Also Toncev et al. found that lower uric acid levels in MS patients are associated with relapse and suggest that uric acid might be beneficial in the treatment of MS (38). Moreover some studies among different populations indicated that patients with MS have low serum levels of the UA, although it has not been established whether UA is primarily deficient or secondarily reduced due to its peroxynitrite scavenging activity (25-29). For the clinician, evaluation of disease from a prognostic view point and efficacy of therapeutic interventions is so important. Our studies suggested that measurement of plasma IL2 and UA concentrations may provide an objective marker of disease in patients with MS. In addition, it seems that studies with larger sample size are required to bring about more authentic results.

4. CONCLUSION

The Plasma concentration of IL2 and UA was significantly higher and lower in MS patients in comparing to controls, respectively. Our studies suggested that measurement of plasma IL2 and UA concentrations may provide an objective marker of disease in patients with MS.

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AUTHORS CONTRIBUTION

This work was carried out in collaboration among all authors.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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