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URIC ACID, A POTENTIAL BIOMARKER OF MULTIPLE SCLEROSIS AND ITS DISABILITY

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ABSTRACT

Background: Multiple sclerosis is an autoimmune chronic disease with two components inflammation and neurodegeneration.. Oxidative stress is implicated in MS pathogenesis, and uric acid, a potent antioxidant scavenger of peroxynitrite, may offer neuroprotection. This study investigates uric acid as a potential biomarker for MS and its association with disability. **Methods:** A prospective case-control study enrolled 100 participants. The MS group (n=50, 13 males, 37 females), comprised individuals diagnosed using established criteria, with a mean age of 34.9 years recruited from the Neurology Department, Tishreen University Hospital, Latakia (April 2023-May 2024). The control group (n=50, 13 males, 37 females), with a mean age of 27.5 years, consisted of individuals without MS or neurological conditions and with no history of medications affecting uric acid levels. Uric acid levels and disability scores were measured. **Results:** The MS group had significantly lower uric acid levels (mean: 3.5 mg/dL) compared to the control group (mean: 4.3 mg/dL) (p-value = 0.01). A negative correlation was observed between uric acid levels and disability scores in MS patients (p-value < 0.05). **Conclusion:** There is an important association between low uric acid levels and increased disability in MS. Large-scale studies are needed to validate these results and explore underlying mechanisms.

KEYWORDS: Multiple sclerosis, EDSS (Expanded Disability Status Scale), peroxynitrite, uric acid.

INTRODUCTION

Multiple sclerosis is a chronic, immune-mediated inflammatory demyelinating disease that affects the white matter of the central nervous system .its pathogenic mechanisms involve several cell types, including lymphocytes, neurons, endothelial cells, monocytes, and glial cells, all of which contribute to the production of inflammatory mediators. Multiple sclerosis affects more than 2millions people worldwide with the highest prevalence through those between the age of 20 and 40 years.[1,2,3]

The involvement of reactive oxygen and detergent species, including nitric oxide and its oxidizing congeners, in the inflammatory demyelination and axonal damage observed in multiple sclerosis (MS), suggests a crucial role for oxidative stress as a potential mechanism of MS its animal model, experimental autoimmune encephalitis (EAE).[3,4]

Growing consensus among experts suggests that peroxynitrite (ONOO-), a harmful product generated by free radical nitric oxide and superoxide, contributes to the pathogenesis of central nervous system inflammatory diseases, including MS.[5]

In its role as the final product of purine metabolism, uric acid acts as a well-known scavenger of peroxynitrite.[6] Notably, treatment with this naturally occurring compound, which selectively binds and neutralizes peroxynitrite, has been shown to inhibit the onset of clinical disease in a severe form of mouse EAE. This result strongly suggests that peroxynitrite is the more toxic molecule involved.[7,8]

Interestingly, strong evidence suggests an association between multiple sclerosis (MS) and lower serum uric acid levels. Uric acid may even serve as a pre-clinical biomarker for the disease.[9] Furthermore, extensive epidemiological studies reveal a nearmutually exclusive relationship between MS and conditions characterized by pathologically elevated uric acid levels, such as gout.[10]

In addition, it has been observed that serum levels of uric acid, thought to play an important role in the

development of neurodegeneration, are lower in MS patients.[11,12,13]

MATERIALS AND METHODS

Study design

This case-control study was designed to elucidate the protective role of serum uric acid levels in multiple sclerosis patients by investigating its association with disability.

Case group

The patients were recruited from the neurology department. Tishreen University Hospital, Latakia, Syria, between April 2023 and May 2024. All cases were diagnosed with MS Based on the revised Mcdonald Criteria 2017. Clinical features of multiple sclerosis cases were evaluated to include the following:

Disease duration (years since the diagnosis), expanded disability status scale (EDSS), disease type (relapsing-remitting, Secondary-progressive, primary-progressive MS, and clinically isolated syndrome),and current disease-modifing treatment (if any).

Medical and medication history were reviewed thoroughly to ensure eligibility.

Patients with current or recent clinical relapse (defined as symptoms or deficits that developed newly for at least 24 hours in the absence of fever or high temperature) treated or not treated with corticosteroids, recently changed disease-modifying treatment (less than six months), or conditions known to affect serum uric acid levels (comorbidities, drugs, alcohol intake, and body mass index) were excluded.

Control group

Controls were recruited during the study period from the same hospital as cases, ensuring similar age ranges and sex distribution. These controls had no medical history or conditions affecting uric acid levels. While some resident doctors were included as controls, efforts were made to include individuals from the general population to minimize potential bias related to lifestyle factors.

Laboratory findings

Serum uric acid concentrations were measured using a colorimetric assay on a Mindray BS-380 analyzer. Reference ranges in our laboratory were 2.6-5.6 mg/dL for women and 3.4-6.4 mg/dL for men.

Statistical analysis

This study employed a combination of descriptive and inferential statistics to analyze the relationships between study variables. To compare the MS patients and control groups we used independent-samples t-tests for continuos variables. To evaluate the association between quality variables, we employed Pearson's correlation coefficient. Finally, chi-square examined the relationships between categorical quality variables. Statistical significance was set at $p < 0.05$.

RESULTS

This study enrolled 100 participants: 50 patients with multiple sclerosis (MS) forming the case group (mean age of 34.9 years; 13 males, 37 females), and 50 healthy controls matched for age, sex, gender, medical history, smoking status and alcohol consumption.

In the case group, there were (32 patients RRMS, 14 SPMS, 2 CIS, and 2 PPMS) and the majority of our case group *were not on* disease-modifying treatment (27 patients), and the rest distributed as 17 patients were on interferon beta, 3 on Rituximab, and three on Teriflunomide.

The disease duration from the onset of the illness ranged from 2 weeks to 30 years, with a mean of 7.3 years. EDSS scores ranged from 0 (no disability) to 8 (requiring an electric wheelchair), with a mean of 3.45Uric acid levels in the control group (mean: 4.3 mg/dl, range: 2.8-6.4 mg/dl) were higher than those in the case group (mean: 3.5 mg/dl, range: 1.4-5.9 mg/dl).

Our analysis revealed significantly lower serum uric acid levels in MS subjects compared than controls (p=0.02). Interestingly, an inverse relationship was observed between EDSS scores and uric acid levels (p=0.008), with the lowest uric acid levels associated with higher EDSS scores. No significant associations were found between uric acid levels and disease duration (p=0.68), disease type (p=0.053), or diseasemodifying treatment (p=0.077).

DISCUSSION

As we have noticed before, Individuals with MS displayed significantly lower levels of uric acid in their blood compared to healthy controls. This difference (3.5 mg/dL vs. 4.3 mg/dL) suggests a potential link between low uric acid and increased disability, as evidenced by the negative correlation between uric acid levels and EDSS scores (p=0.008).

These findings suggest uric acid levels might be a potential biomarker for MS disease activity. Lower uric acid could be associated with increased inflammatory processes or impaired antioxidant mechanisms in MS patients with higher disability scores. However, further research is needed to explore the underlying mechanisms and potential causal relationships.

Our study has limitations. Our findings may not be applicable to the broader population due to the limited sample size. Additionally, excluding patients with recent relapses could have excluded a potentially informative subgroup. Future studies with more extensive and more diverse patient populations, including those with recent relapses, are needed to confirm our findings. Radiological assessments could also provide valuable

insights into the relationship between uric acid and disease activity in MS.

In conclusion, our study suggests that serum uric acid levels may serve as a potential biomarker for multiple sclerosis (MS) and its associated disability. We observed a statistically significant decrease in uric acid levels in MS patients compared to controls, with lower levels correlating with more excellent disability scores. This finding aligns with the potential protective role of uric acid as a potent antioxidant, potentially mitigating some of the oxidative stress mechanisms involved in MS pathogenesis. However, further research with more extensive and more diverse patient populations is warranted to elucidate the underlying mechanisms and explore the potential of uric acid as a therapeutic target in MS.

REFRENCES

1. Huang, W.J.; Chen, W.W.; Zhang, X. Multiple sclerosis: Pathology, diagnosis and treatments. Exp. Ther. Med., 2017; 13: 3163–3166. [CrossRef]
2. Dilokthornsakul, P.; Valuck, R.J.; Nair, K.V.; Corboy, J.R.; Allen, R.R.; Campbell, J.D. Multiple sclerosis prevalence in the United States commercially insured population. Neurology, 2016; 86: 1014–1021. [CrossRef] [PubMed]
3. Schreibelt G, van Horssen J, van Rossum S, Dijkstra CD, Drukarch B, de Vries HE. Therapeutic potential and biological role of endogenous antioxidant enzymes in multiple sclerosis pathology. Brain Res Rev., 2007; 56: 322–30.
4. Bagasra O, Michaels FH, Zheng YM, Bobroski LE, Spitsin SV, Fu ZF *et al.* Activation of the inducible form of nitric oxide synthase in the brain of the patients with multiple sclerosis. *Proc Natl Acad Sci USA*, 1995; 92: 12041–45.
5. Hooper DC, Scott GS, Zborek A, Mikheeva T, Kean RB, Koprowski H, et al. Uric acid, a peroxynitrite scavenger, inhibits CNS inflammation, blood–CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis. FASEB J., 2000; 14: 691–8.
6. Hooper DC, Bagasra O, Marini JC, Zborek A, Ohnishi ST, Kean R *et al.* Prevention of experimental allergic encephalo-myelitis by targeting nitric oxide and peroxynitrite: implications for the treatment of multiple sclerosis. *Proc Natl Acad Sci USA*, 1997; 94: 2528–33.
7. Whiteman M and Halliwell B. Protection against peroxynitrite-dependent tyrosine nitration and alpha 1antiproteinase inactivation by ascorbic acid. A comparison with other biological antioxidants. Free Radic Res., Sep. 1996; 25(3): 275–283.
8. Hooper DC, Bagasra O and Marini JC, et al. Prevention of experimental allergic encephalomyelitis by targeting nitric oxide and peroxynitrite: Implications for the treatment of multiple sclerosis. Proc Natl Acad Sci U S A., Mar. 18, 1997; 94(6): 2528–2533.
9. Rumbach L. EDSS expanded disability status scale. Rev Neurol (Paris), 2000; 156: 1036–40. French.
10. Hooper DC, Bagasra O, Marini JC, Zborek A, Ohnishi ST, Kean R, et al. Prevention of experimental allergic encephalomyelitisby targeting nitric oxide and peroxynitrite: implications for the treatment of multiple sclerosis. Proc Natl Acad Sci USA, 1997; 94: 2528–33.
11. Liu B, Shen Y, Xiao K et al. Serum uric acid levels in patients withmultiple sclerosis: a meta-analysis. Neurol Res., 2012; 34(2): 163–171.
12. Guerrero AL, Gutiérrez F, Iglesias F et al. Serum uric acid levels in multiple sclerosis patients inversely correlate with disability. Neurol Sci., 2011; 32(2): 347–350.
13. Maesaka JK, Wolf-Klein G, Piccione JM et al. Hypouricemia, abnormal renal tubular urate transport, and plasma natriuretic factor (s) in patients with Alzheimer's disease. J Am Geriatr Soc., 1993; 41(5): 501–506.