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ORIGINAL ARTICLE

The Relation between Uric Acid and Epilepsy

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ABSTRACT

Background: The close link between oxidative stress and neuroinflammation is greatly implicated in the pathogenesis of epilepsy. There is evidence that uric acid with its pro-inflammatory and pro-oxidant potentials leads to increased excitability, enhancing the severity of epileptic seizures. The current study aimed to assess the association between serum uric acid level and disease characteristics and evaluate the effect of antiepileptic drugs on its level.

Methods: This study was done on 62 healthy subjects and 62 patients with primary epilepsy, subjected to detailed medical and neurological history taking with stress on the seizure history (especially seizure frequency and seizure control and current antiepileptic drugs), and laboratory evaluation of serum uric acid.

Results: High levels of uric acid were found in epileptic patients compared to healthy subjects. Higher levels of serum uric acid were associated with the clinical parameters: more disease duration, more seizure frequency and severity, and in patients receiving polytherapy and patients with poor seizure control.

Conclusions: Uric acid can be used as a biomarker of oxidative stress and neuroinflammation which are involved in the pathogenesis of epilepsy. Therefore, manipulating uric acid can be beneficial in suppressing epileptic seizures.

Keywords: Uric acid, seizures, epilepsy, antiepileptic drugs

INTRODUCTION

Epilepsy is one of the top five neurological diseases with the highest burden of disease [1]. It is characterized by an imbalance between neural excitability and inhibition, leading to recurrent spontaneous seizures [2]. Neuroinflammation and increased oxidative stress are involved in the epileptogenesis and play a role in determining seizure threshold in animal models. They are tightly interrelated and reinforce each other [3].

Due to its pro-inflammatory and pro-oxidant properties, increased uric acid levels have been related to cardiovascular disease which is a significant cause of the high risk of premature death in epilepsy [4-6].

Uric acid is a nonenzymatic hydrophilic antioxidant with most of the oxygen scavenging in the serum [7]. It is produced during the metabolism of dietary and endogenous purines [8]. The antioxidant action of uric acid is restricted to the hydrophilic environment. However, its crystallized form in the hydrophobic environment acts as a danger associated molecular patterns (DAMPs) in several disorders with prooxidant and proinflammatory actions [9-12].

The high level of uric acid is linked to gout, inflammatory arthritis, hypertension, cardiovascular diseases, schizophrenia and bipolar disorder, and may enhance severity of epileptic seizures [7, 13].

The systemic increase in uric acid levels after status epilepticus is explained by the hypermia and sweating which are associated with the seizures, leading to excess muscle breakdown and changed renal secretion [14]. However, the seizure itself and

the resulted neuronal injury and blood-brain barrier leakage lead to the increased uric acid level in the brain [15,16].

This study aimed to assess the serum uric acid level in epilepsy and explore if there is a relationship between it and disease characteristics and if the effect of antiepileptic drugs on such parameters could be observed.

METHODS

This case-control study included 62 patients with primary (idiopathic) epilepsy, 36 men and 26 women, ranging in age from 18 to 45, and who attended the Neurology department (outpatient clinic) at Zagazig University and Al-Ahrar Zagazig Teaching Hospitals after obtaining the required authorities' permissions, during the period from April 2020 to December 2020. The case group was matched for age and gender with a control group of 62 healthy people, 35 males and 27 females.

Written informed consent was obtained from all participants. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The Ethical Committee of Zagazig University's Faculty of Medicine gave their approval to the study's design (ZU-IRB # 6007/9-3-2020).

Smokers, pregnant, lactating moms, significant psychiatric comorbidity, people with acute or chronic medical illness, or other factors that may affect the oxidative stress, like malignancy and metabolic abnormalities, were excluded from both the control and epilepsy groups. Symptomatic epilepsy patients with abnormal neurological examination or abnormal neuroimaging, patients with cerebral palsy, history of CNS infection, and post stroke were also excluded.

All the patients underwent a complete medical history and examination, with stress on the seizure history as duration of illness, treatments either mono or polytherapy, seizure control either controlled or uncontrolled according to the response to treatment, and current seizure frequency for the uncontrolled cases. The diagnosis of the epilepsy was done according to the International League Against Epilepsy (ILAE) 2017 classification system [17,18].

Uncontrolled seizures were defined as the inability to attain prolonged seizure absence for minimum one year after sufficient trials of two well-tolerated, well-chosen antiepileptic regimens (as solely or in combinations). The controlled seizure was defined as complete seizure freedom for at least one year [19].

Severity of epilepsy is measured according to the Liverpool Seizure Severity Scale [20]. The scale describes how the patient perceives the seizure effect on his everyday life.

All patients underwent electroencephalography (EEG), neuroimaging for a definitive diagnosis, and measuring the serum level of the currently used AED. Laboratory investigation of serum uric acid level was done for all patients and control group.

Statistical analysis

The IBM SPSS software package version 20.0 was used to analyze the data on the computer. Numbers and percent were used to describe qualitative data. To ensure that the distribution was normal, the Kolmogorov-Smirnov test was applied. Range (minimum and maximum), mean and standard deviation were used to describe quantitative data. The significance of the observed results was determined at a 5% level of significance. The used tests were Chi-square test, Student t-test, ANOVA and Pearson correlation coefficient.

RESULTS

The case and control group had no differences as regard demographic data (Table 1). There was statistically highly significant increase in mean values of uric acid in epileptic group compared to control group (Table 1).

Among the epileptic group, the mean age of onset was 17.85 years (±4.64 SD), the mean disease duration was 13.11 years (±8.19 SD), 21 (33.9%) patients with focal and 41 (66.1%) with generalized seizure, 26 (41.9%) were well controlled and 36 (58.1%) uncontrolled. According to seizure frequency of uncontrolled patients, there were 10 (27.8%) patients with seizures more than once per month, 14 (38.9%) with once per 1-2 months, 7 (19.4%) with once per 3-4 months and 5 (13.9%) with once per 5-6 months. According to type of therapy, there were 27 (43.5%) patients with monotherapy and 35 (56.5%) with polytherapy. According to EEG findings, there were 6 (9.7%) patients with focal epileptogenic activity, 12 (19.4%) with focal to 2ry generalization, 22 (35.5%) with generalized epileptogenic activity and 22 (35.5%) normal. The mean Liverpool score of the epileptic group was 52.15 (±6.23 SD) with range (40-66).

There were considerable positive relations between uric acid and age and seizure frequency (Table 2) (Figure 1). In the epileptic group, there

was a strong association between Liverpool score and uric acid (Table 2) (Figure 2). There was a positive association between serum carbamazepine (CBZ) and uric acid in the epileptic group, but no such correlation existed between valproic acid (VPA) and uric acid (Table 2).

There was considerable elevation in uric acid in patients with disease duration >5years compared to disease duration ≤ 5 years (Table 3).

The comparison between controlled and uncontrolled patients as well as healthy controls showed higher levels of uric acid in patients with poor seizure control than those with controlled seizure and healthy control group (Table 4).

The comparison between patients on single drug (monotherapy) and those patients on more than one drug(polytherapy) showed higher levels of uric acid in patients receiving polytherapy than those on monotherapy and healthy controls (Table 4).

Table (1): Data about the studied individuals' demographics and laboratory results

	Epileptic group (n=62)		Controls group (n=62)		test	p	Sig.
Age (years)							
Mean ± SD	27.98 ± 6.44		26.63 ± 6.06		t=1.207	0.230	NS
Range	18.0 – 43.0		19.0 – 39.0				
Sex	**No.**	**%**	**No.**	**%**			
Male	36	58.1	35	56.5	χ^2=0.033	0.856	NS
Female	26	41.9	27	43.5			
Uric acid (mg/dl)							
Mean ± SD	5.85 ± 1.20		3.38 ± 0.66		14.197	<0.001*	HS
range	3.50 – 7.90		2.50 – 5.0				

t: Student t-test; χ^2: Chi square test; p: p value for comparing between the studied groups; NS: nonsignificant; HS: highly significant.

Table (2) : Correlation between uric acid and some seizure characteristics and serum drug level of VPA&CBZ

	Uric acid (mg/dl)	
	r	p
Age	0.390	0.002*
Age of onset	-0.096	0.459
Seizure frequency	0.436	0.008*
Liverpool score	0.455	<0.001*
VPA (mg/dl)	0.048	0.773
CBZ (mg/dl)	0.617	0.005*

CBZ: carbamazepine; VPA: valproic acid.
r: Pearson coefficient; *: Statistically significant at p ≤ 0.05

Table (3): Relations between uric acid and disease duration

	≤ 5 years (n=15)	> 5 years (n=47)	t	P	Sig.
Uric acid (mg/dl)					
Mean ± SD	5.29 ± 1.37	6.02 ± 1.09	2.133	0.037*	S
range	3.50 – 7.50	3.70 – 7.90			

t: Student t-test; SD: standard deviation; S: Significant

Table (4): Comparison between patient subgroups (controlled & uncontrolled) & (mono & polytherapy) and controls group regarding uric acid.

	Uric acid (mg/dl)			
	Mean ± SD	F	P	Sig.
Uncontrolled patients (n=36)	6.48 ± 0.79	171.265	<0.001*	HS
Controlled patients (n=26)	4.96 ± 1.10			
Healthy Controls (n=62)	3.38 ± 0.66			
monotherapy Patients (n=27)	4.99 ± 1.1	172.482	<0.001*	HS
polytherapy patients (n=35)	6.51 ± 0.78			
Healthy Controls (n=62)	3.38 ± 0.66			

F: ANOVA test; SD: standard deviation; HS: highly significant

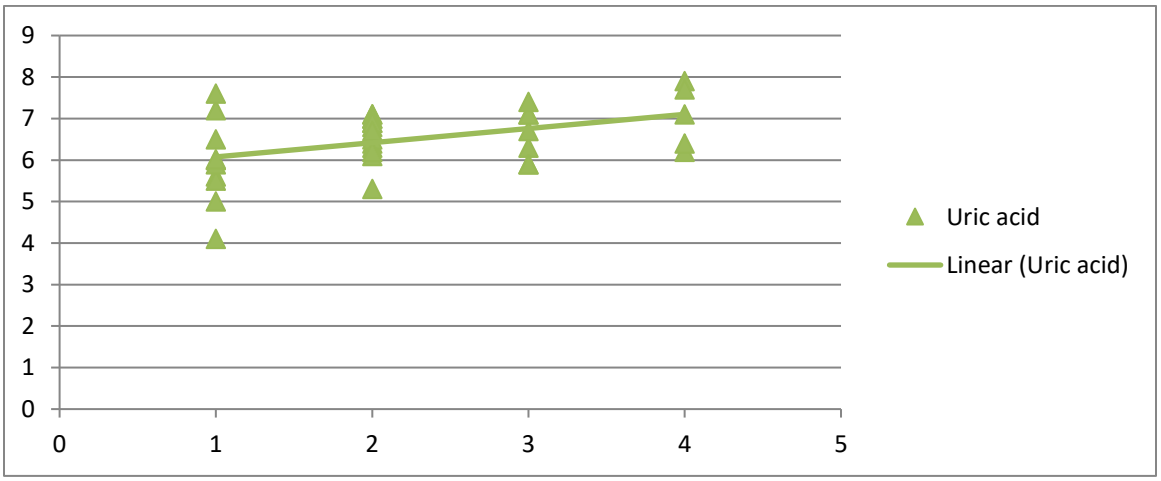

Fig (1): Correlation between Seizure frequency and uric acid of epileptic group

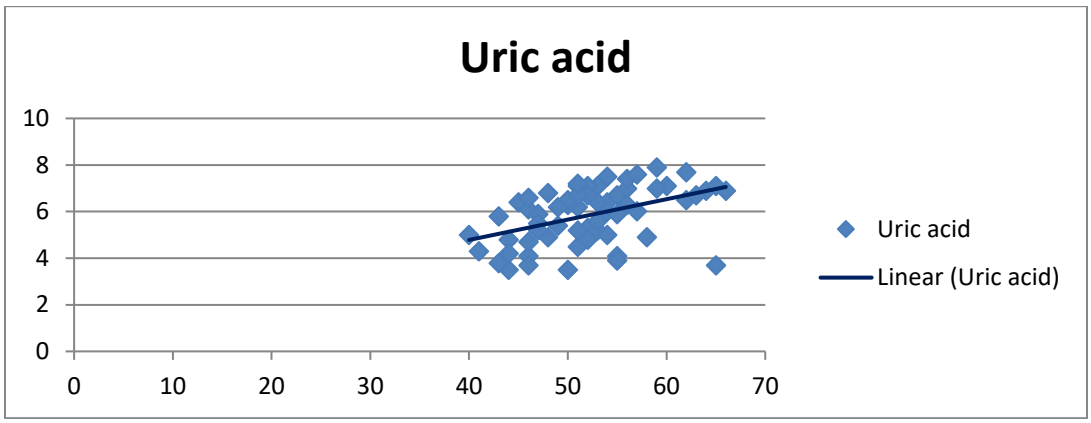

Fig (2): Correlation between Liverpool score and uric acid of epileptic group

DISCUSSION

Uric acid is a nonenzymatic hydrophilic antioxidant [21]. Its action is a paradox. While its soluble form in plasma is an antioxidant, its crystallized form within the cell is a pro-oxidant triggering an inflammatory response leading to an increased excitability [22, 23]. There are debates about the uric acid as antioxidant or oxidative stress biomarker [24].

In the current study, we did a comparison between the epileptic patients and controls regarding the uric acid serum level as it contributes to epileptogenesis by being implicated in inflammatory and oxidative processes. In this study, there was statistically highly significant increase in mean values of uric acid in epileptic group compared to control group despite being within the normal range.

Earlier studies revealed that seizures could result in elevation of uric acid levels in serum [25, 26] and in cerebrospinal fluid of epileptics [27]. Experimental studies showed increased uric acid in the brain during seizures [13, 28].

Similarly, **Jiang et al.** [29] reported that serum level of uric acid was significantly elevated in the group with generalized tonic–clonic seizures than in the groups with syncope and psychogenic nonepileptic seizures.

In accordance with our results, a cohort study in Taiwan revealed that the epilepsy overall incidence was 1.27-fold more in the gout group (with hyperuricemia) compared with the control group [30].

In contrast, there was not significant difference between epileptics and controls as regard uric acid serum levels [31, 32].

Uric acid could contribute to seizure susceptibility. It rises after seizures and can stay high in those with chronic epilepsy. It plays a role in epileptogenesis by participating in inflammatory and oxidative processes. Furthermore, allopurinol, a uric acid inhibitor, has antiseizure-properties [13, 27, 28, 33].

However, the high uric acid level observed by **Hamed et al.** [34] and **Aycicek and Iscan** [35] among the untreated epileptic group argued to the compensatory system against lowered antioxidant potentials and elevated peroxidative injury encountered in epilepsy.

On studying the relation between uric acid level and seizure profile, we found a positive association between it and seizure frequency and Liverpool score. Our patients' seizure severity was measured using the **Liverpool Seizure Severity Scale** [20]. The scale components describe how the patient perceives the burden of seizures on everyday life. Severity is indicated by higher scores.

This finding is in line with **Thyrion et al.** [13] who found that the generalized seizures' number was reduced by twice when allopurinol, a uric acid synthesis inhibitor, was given. Moreover, knocking off urate oxidase, the enzyme accountable for uric acid degradation, led in a double rise in the seizures' number.

Hence, controlling uric acid can be particularly beneficial in preventing secondary generalisation of seizures. Allopurinol has been shown to be effective in reducing the generalised seizures' severity in cats [36] and inhibiting secondary generalised seizures in EL mice [37].

In addition, **Lakatos et al**. [38] reported that in the Wistar Albino Glaxo/Rijswijk rat, uric acid enhanced the number of spike-wave discharging of absence epileptic behavior. Thus, regular uric acid checking and keeping it within the average limits could be useful.

In contrast, **Lorigados Pedre et al.** [2] showed that patients with partial complex seizures had no relation between uric acid levels and the number of seizures / month, or the quantity of medications used.

On stratifying our epileptic patients based on disease duration (> 5 years and ≤ 5 years duration) and studying the relation between disease duration and laboratory findings, the mean uric acid values increased significantly in patients with disease duration >5years compared to disease duration ≤ 5 years.

Similarly, **Krause et al**. [39] found that long-term antiepileptic treatment was linked to uric acid alterations.

When studying the influence of seizure control on uric acid levels, we did a comparison between controlled and uncontrolled epileptics as well as healthy controls. Higher levels of uric acid were recorded in patients with poor seizure control than those with controlled seizures and healthy control group.

In contrast, in drug-resistant partial complex seizure patients, uric acid levels were found to be considerably lower than in controls [2].

To study the effect of antiepileptic drugs, if any, on oxidative stress parameters, we made a comparison between patients on single drug (monotherapy) and those patients on more than one drug (polytherapy) regarding the uric acid. Higher levels of uric acid were observed in patients receiving polytherapy than those on monotherapy and healthy controls.

Similarly**, a**ntiepileptic polytherapy was observed by **Beghi et al.** [40] to induce a considerable increase in serum uric acid levels.

Attilakos et al. [41] reported that VPA as a single drug had no consequence on serum uric acid concentration in walking epilepsy children, both early and late in treatment.

In this study, there was a positive association between serum CBZ levels and uric acid in the epileptic group, however no such relation was noted between VPA levels and the uric acid. This finding may be attributed to that the serum drug level was assessed in the patients taking VPA / CBZ as either monotherapy or polytherapy.

In contrast, patients on enzyme-inducing antiepileptic medications had less uric acid values than those receiving VPA therapy [39].

Ring et al. [42] found that monotherapy with phenytoin and CBZ resulted in a decrease in plasma uric acid, but phenobarbitone and VPA resulted in an increase in this purine byproduct in recently diagnosed patients with epilepsy.

Fichsel et al. [43] and **Pylvanen et al.** [44] reported that patients who took VPA had greater uric acid values than control participants.

Despite being within the average ranges, uric acid levels in VPA-treated patients were considerably higher in previous studies [34, 45]. This could be linked to AED-induced changes in renal secretion or a neuronal defensive reaction to peroxidative injury.

On the other hand, **Yoshikawa et al.** [46] found that the serum uric acid values were reduced in non-ambulatory patients who took VPA, but not in ambulatory patients. This is due to the possibility of VPA-caused renal tubular impairment in profoundly handicapped children.

CONCLUSIONS

In this study, we observed that epileptic patients had greater values of serum uric acid than healthy individuals. Higher values of serum uric acid were linked to the clinical parameters: more disease duration, more seizure frequency and severity, and in patients receiving polytherapy and patients with poor seizure control. Thus, regular uric acid checking and keeping it in the average limits could be advantageous. Future research should focus on uric acid as a therapeutic target in epilepsy.

Conflict of interest: No

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