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The value of serum uric acid levels to differentiate causes of transient loss of consciousness

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ABSTRACT

Background: Generalized tonic–clonic seizures (GTCS), syncope, and psychogenic nonepileptic seizures (PNES) are common emergent neurological conditions that cause transient disturbances of consciousness; however, it is sometimes difficult to distinguish them.
Objective: This study aimed to explore the value of serum uric acid levels in differentiating among GTCS, syncope, and PNES by analyzing serum uric acid levels in patients with GTCS, syncope, and PNES.
Methods: A total of 391 patients were retrospectively analyzed. Venous blood was drawn from the patients within 20 min of their arrival to the emergency department; serum uric acid levels were measured using the uricase method.
Results: Serum uric acid levels and the percentage of patients with elevated uric acid (elevation percentage) were significantly higher in the group with GTCS ($n = 179$) than in the groups with syncope ($n = 156$) ($p < 0.001$) and PNES ($n = 56$) ($p < 0.001$). The result remained the same when the serum uric acid level of male or female patients in the group with GTCS were compared separately with that in the other two groups (all $p < 0.001$). In the group with GTCS, both the serum uric acid level ($p < 0.001$) and elevation percentage ($p < 0.05$) were significantly higher in males than in females. The receiver operating characteristics (ROC) analysis in male patients yielded a serum uric acid value of 428.50 μmol/L with a sensitivity of 0.78 and a specificity of 0.99 as the optimal cutoff value to distinguish GTCS from other events. In female patients, a cutoff value of 338.00 μmol/L had a sensitivity of 0.69 and a specificity of 0.91 to distinguish GTCS from other events. For the group with GTCS, the period of time between the onset of seizure and serum uric acid levels dropping to normal were analyzed in 40 patients. The duration was 44.56 ± 11.46 h for males ($n = 23$) and 40.37 ± 9.78 h for females ($n = 17$) with no significant difference ($p = 0.325$).
Conclusion: Serum uric acid levels provided certain clinical value for the differentiation of GTCS, syncope, and PNES; however, this requires verification in prospective studies with larger sample sizes.

1. Introduction

Generalized tonic–clonic seizures (GTCS), syncope, and psychogenic nonepileptic seizures (PNES) are common conditions in neurological emergencies [1], all of which can manifest as transient disturbances in consciousness. However, differential diagnosis among them is sometimes difficult, and the rate of misdiagnosis can be as high as 20–30% [2].

Currently in the emergency department, the differentiation among GTCS, syncope, and PNES is mainly based on medical history [3]; however, approximately 12% of patients with syncope can present with convulsive syncope [4]. The clinical manifestations of PNES and GTCS are also similar, which further increases the difficulty of diagnosis. Meanwhile, because of the loss of consciousness of the patients and the absence of witnesses, it is exceedingly difficult to determine the onset of disease. Even if witnesses are present, they usually cannot accurately describe the situation at the time of onset because of nervousness and lack of medical expertise. This leads to incomplete or inaccurate information when physicians attempt to collect medical history, which in turn hinders timely and correct diagnosis. Electroencephalogram (EEG) and upright tilt testing can be used for distinguishing the three conditions; however, they are inconvenient in emergency settings, and the positive rate is not high [4]. Moreover, for EEG, the results of patients with epilepsy can be normal, and sometimes the results of patients without epilepsy are abnormal [5]. However, the pathogenesis, treatment, and prognosis of the three conditions are quite different; therefore, timely and accurate diagnosis is particularly important. If a serum marker is available for differentiation among GTCS, syncope, and PNES, it would be convenient in emergent situations requiring quick diagnosis. Although Paulson found that serum uric acid levels were significantly elevated during seizures [6], there have been few follow-up studies. There have been no relevant reports describing the

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value of serum uric acid levels in the differential diagnosis among GTCS, syncope, and PNES. Accordingly, in the present study, we performed a series of analyses, focusing especially on sex differences.

2. Material and methods

2.1. Study design and population

A retrospective analysis of patients who visited the Neurology Emergency Department of Beijing Jishuitan Hospital (Beijing, China), and were diagnosed with GTCS, syncope, or PNES between November 2012 and September 2018, was performed. Subjects were selected from among patients who experienced typical episodes that were confirmed by experts in related fields based on clinical manifestation(s), medical history, and related auxiliary examinations. Patients with history of hyperuricemia, gout, renal insufficiency, or other history of diseases affecting serum uric acid levels, or taking medications that may affect uric acid excretion, were excluded.

Venous blood from all subjects was drawn within 20 min of patient arrival to the emergency department; serum uric acid levels were measured using the uricase method (normal ranges for uric acid, male <428 μmol/L; female <357 μmol/L). The study was approved by the Ethics Committee of Beijing Jishuitan Hospital.

2.2. Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 19.0 (IBM Corporation, Armonk, NY, USA). Blood sampling time, age, serum uric acid levels, follow-up time, and the period of time between the onset of seizure and serum uric acid levels dropping to normal were expressed as mean ± standard deviation (SD). The means of the three groups were compared using one-way analysis of variance. The means of the group with GTCS and group without epilepsy were compared using the t test. The enumeration data were expressed as number of cases (%), and the χ^2 test was used to compare the groups. A receiver operating characteristics (ROC) analysis was used to plot the points of sensitivity and specificity for various serum uric acid levels on sex differences. The optimal cutoff value was determined via the Youden index. The area under the curve (AUC) was considered a measure for the discriminatory power of serum uric acid level. Pearson correlation analysis was performed, and the paired t test was used to compare serum uric acid levels before and after follow-up. The means of the duration between the onset of seizure and serum uric acid levels dropping to normal for different sexes were compared using the t test.

3. Results

A total of 391 patients were enrolled in the study, including 179 in the group with GTCS (131 males, 48 females), 156 in the group with syncope (75 males, 81 females), and 56 in the group with PNES (26 males, 30 females). The period of time between the onset of the disease and blood sampling was 2.17 ± 1.13 h for the group with GTCS, 1.92 ± 0.89 h for the group with syncope, and 2.34 ± 1.27 h for the group with PNES. There was no significant difference in age or blood sampling time among the groups (Table 1).

Table 1
Comparison of age and blood sampling time among the different groups.

Diagnosis	Age (years)	Blood sampling time[a] (h)
GTCS (n = 179)	49.7 ± 21.6	2.17 ± 1.13
Syncope (n = 156)	51.3 ± 24.1	1.92 ± 0.89
PNES (n = 56)	45.7 ± 18.6	2.34 ± 1.27
Not GTCS (syncope or PNES) (n = 212)	48.8 ± 20.7	2.11 ± 1.07

Data presented as mean ± standard deviation. GTCS, generalized tonic–clonic seizures; PNES, psychogenic nonepileptic seizures.
[a] Refers to the period of time between the onset of the disease and blood sampling.

Table 2
Comparison of serum uric acid levels and elevation percentage among different groups.

Diagnosis	Serum uric acid level (μmol/L), mean ± SD	Elevation percentage, n (%)
GTCS (n = 179)	510.97 ± 194.22	127(70.95)
Syncope (n = 156)	306.22 ± 75.90	10(6.41)
PNES (n = 56)	284.21 ± 55.38	1(1.79)
Not GTCS (syncope or PNES) (n = 212)	300.41 ± 71.59	11(5.19)

GTCS, generalized tonic–clonic seizures; PNES, psychogenic nonepileptic seizures.

The serum uric acid level in the group with GTCS was 510.97 ± 194.22 μmol/L, and 127 (70.95%) patients had elevated serum uric acid levels (Table 2). The serum uric acid level in the group with syncope was 306.22 ± 75.90 μmol/L, and 10 (6.41%) patients exhibited elevated serum uric acid levels. The serum uric acid level was 284.21 ± 55.38 μmol/L in the group with PNES, and 1 (1.79%) patient exhibited an elevated serum uric acid level. The serum uric acid level was 300.41 ± 71.59 μmol/L in the group without epilepsy (syncope and PNES), and 11 (5.19%) patients exhibited elevated serum uric acid levels. The serum uric acid level in the group with GTCS was significantly higher than that in the groups with syncope ($p < 0.001$) and PNES ($p < 0.001$). The serum uric acid level in the group with GTCS was significantly higher than that in the group without epilepsy ($p < 0.001$). There was no significant difference in serum uric acid levels between the group with syncope and the group with PNES ($p = 0.319$). The elevation percentage in the group with GTCS was also significantly higher than that in the group with syncope and the group with PNES ($p < 0.001$). Similarly, the elevation percentage in the group with GTCS was significantly higher than that in the group without epilepsy ($p < 0.001$). There was no significant difference in the elevation percentage between the group with syncope and the group with PNES. When serum uric acid levels and the elevation percentages of male and female patients were compared separately among the three groups, the results remained the same. Regardless of sex (male [Table 3] or female [Table 4]), both serum uric acid levels and elevation percentages were significantly higher in the group with GTCS than in the groups with syncope ($p < 0.001$) and PNES ($p < 0.001$). Similarly, the same parameters were significantly higher in the group with GTCS than in the group without epilepsy ($p < 0.001$), regardless of sex, and there was no significant difference between the groups with syncope and PNES.

For the group with GTCS, serum uric acid levels ($p < 0.001$) and elevation percentage ($p < 0.05$) were significantly higher in males than in females (Table 5), and there was no significant difference in age between the two sexes ($p = 0.137$).

The ROC analysis in male patients yielded a serum uric acid value of 428.50 μmol/L with a sensitivity of 0.78 and a specificity of 0.99 as the optimal cutoff value to distinguish GTCS from other events (Fig. 1). The ROC analysis for AUC yielded a high estimate of 0.91 (95% confidence interval: 0.88–0.95). In female patients, the ROC curve analysis had a lower estimate of AUC that was 0.81 (95% confidence interval: 0.73–0.90). A cutoff value of 338.00 μmol/L had a sensitivity of 0.69 and a specificity of 0.91 to distinguish GTCS from other events.

Table 3
Comparison of serum uric acid levels and elevation percentage among male patients.

Diagnosis	Serum uric acid level (μmol/L), mean ± SD	Elevation percentage, n (%)
GTCS (n = 131)	559.53 ± 187.76	99(75.57)
Syncope (n = 75)	340.57 ± 72.75	4(5.33)
PNES (n = 26)	308.12 ± 56.58	1(3.85)
not GTCS (syncope or PNES) (n = 101)	332.22 ± 70.14	5(4.95)

GTCS, generalized tonic–clonic seizures; PNES, psychogenic nonepileptic seizures.

Table 4
Comparison of serum uric acid levels and elevation percentage among female patients.

Diagnosis	Serum uric acid levels (μmol/L), mean ± SD	Elevation percentage, n (%)
GTCS (n = 48)	378.46 ± 144.35	28(58.33)
Syncope (n = 81)	274.42 ± 64.30	6(7.41)
PNES (n = 30)	263.50 ± 45.84	0(0)
not GTCS (syncope or PNES) (n = 111)	271.47 ± 59.87	6(5.41)

GTCS, generalized tonic–clonic seizures; PNES, psychogenic nonepileptic seizures.

Table 5
Comparison of serum uric acid levels and elevation percentages between the two sexes in the generalized tonic–clonic seizures group.

Sex	Age (years)	Serum uric acid levels (μmol/L) mean ± SD	Elevation percentage, n (%)
Male (n = 131)	51.2 ± 22.4	559.53 ± 187.76	99(75.57)
Female (n = 48)	48.8 ± 20.7	378.46 ± 144.35	28(58.33)

Serum uric acid levels were negatively correlated with age in the group with GTCS ($p = 0.000$, $r = -0.261$), and there was no significant correlation between the two in the groups with syncope and PNES ($p = 0.664$, $p = 0.180$).

A follow-up of serum uric acid levels was performed in some patients (Table 6), including 40 in the group with GTCS, 27 in the group with syncope, and 12 in the group with PNES. Serum uric acid level was significantly lower in the group with GTCS than it was before follow-up ($p < 0.001$). There were no significant changes in serum uric acid levels in the groups with syncope ($p = 0.365$) and PNES ($p = 0.532$). There was no significant difference in follow-up time among the three groups ($p = 0.236$). For the group with GTCS, we analyzed the period of time between the onset of seizure and serum uric acid levels dropping to normal. The 40 patients with GTCS included 23 males and 17 females. The duration was 44.56 ± 11.46 h for males and 40.37 ± 9.78 h for females with no significant difference ($p = 0.325$).

Table 6
Comparison of serum uric acid levels before and at follow-up in some patients.

Diagnosis	Serum uric acid level (μmol/L)		Follow-up time[a] (h)
	First visit	Follow-up	
GTCS (n = 40)	489.95 ± 171.03	327.93 ± 138.94	38.29 ± 16.76
Syncope (n = 27)	320.00 ± 62.57	315.89 ± 63.64	43.86 ± 20.35
PNES (n = 12)	292.08 ± 45.99	286.92 ± 39.09	41.67 ± 17.34

Data presented as mean ± standard deviation. GTCS, generalized tonic–clonic seizures; PNES, psychogenic nonepileptic seizures.
[a] Refers to the period of time between the onset of the disease and follow-up.

4. Discussion

Transient loss of consciousness is a common condition in neurological emergencies, in which epilepsy (primarily GTCS), syncope, and PNES account for >90% of the causes [7,8]. Epilepsy is a transient malfunction of the central nervous system caused by repeated abnormal discharges by neurons in the brain. Syncope is transient loss of consciousness due to transient ischemia in the cerebral cortex with various causes. Psychogenic nonepileptic seizures are primarily a psychological disorder. Timely and accurate diagnosis is sometimes not easy because of the absence of witnesses, or because witnesses cannot accurately recall or describe the onset of illness. For example, the clinical onset of PNES is extremely similar to GTCS, which may lead to misdiagnosis [9]. However, there is a significant difference in the treatment and prognosis of the three conditions. For epilepsy, in particular, misdiagnosis may prevent the patient from timely and appropriate treatment, resulting in repeated attacks and even the risk for accidents. The current gold standards for diagnosis are mainly video-EEG and EEG recordings at the time of onset. However, in clinical practice, it is often difficult to accurately capture the abovementioned records of onset. Therefore, in emergency settings, clinical diagnosis is primarily based on the medical history provided by witnesses (if any), as well as examinations including electrocardiogram, head computed tomography, or magnetic resonance imaging, and there is a certain degree of limitation to such diagnostic strategies.

Uric acid is the end product of the metabolism of purines in the human body. Serum uric acid levels increase when the production of uric acid increases or excretion decreases. Previous studies have suggested [6,10,11] that seizures can cause an increase in uric acid

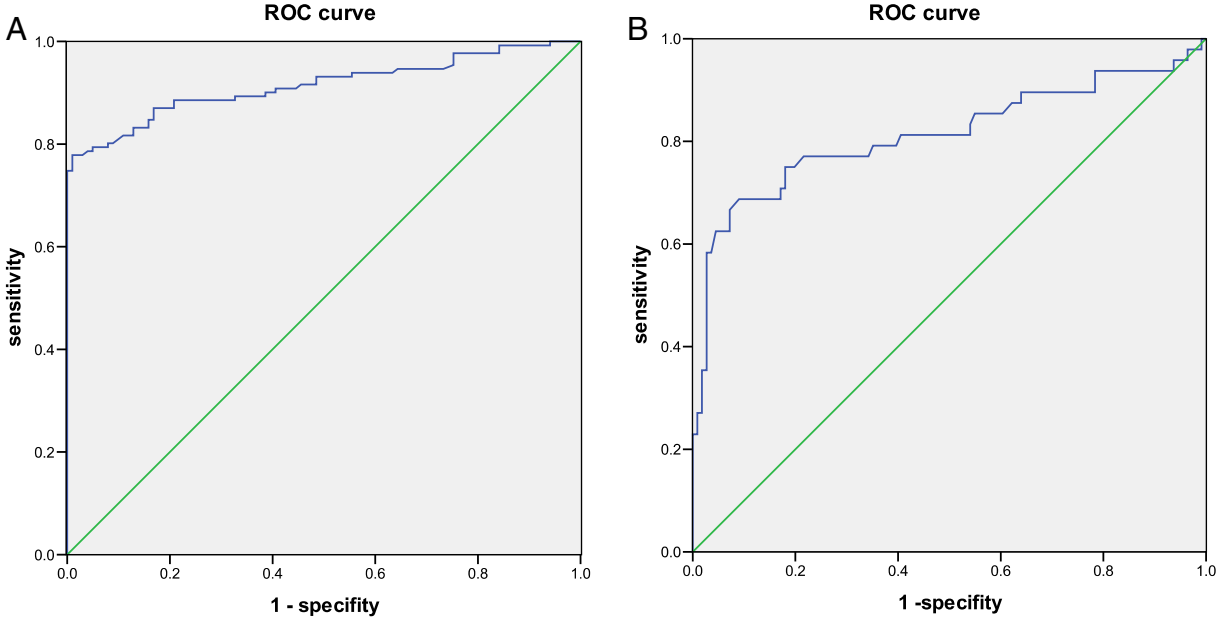

Fig. 1. ROC analyses for serum uric acid level as a marker for the presence of generalized tonic–clonic seizure. A. Male patients. B. Female patients.

production in the body, leading to elevated serum uric acid levels. While other investigations have reported elevated levels of uric acid in the cerebrospinal fluid of patients with epilepsy [12]. Animal experiments [13,14] have also revealed elevated levels of uric acid in the brain during episodes of seizures. Hamed et al. [15] found that serum uric acid levels were significantly lower in patients with epilepsy treated with carbamazepine compared with untreated patients with epilepsy. Some studies [16,17] have also suggested that the drug used to treat hyperuricemia, allopurinol, has a certain effect on refractory epilepsy, indicating that uric acid is not just an epiphenomenon but might actively contribute to the underlying pathophysiology. Although these studies indicate that uric acid and epilepsy are closely related, the specific mechanism remains unclear. Some studies found that high uric acid concentrations easily form monosodium crystals, which can trigger the inflammatory response that can lead to an increased excitability [18]. The downstream components of uric acid in the inflammatory signaling pathway, including caspase-1 [19] and nucleotide binding and oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) [20], can also affect seizure characteristics in animal models for epilepsy. Notably, this pathway leads to the activation of interleukin-1β (IL-1β), a central proinflammatory cytokine involved in excitability [21].

Syncope is mainly caused by a transient ischemia in the cerebral cortex, which lasts only a short time, with no obvious metabolic abnormality in the brain; therefore, the possibility of uric acid elevation is low. Psychogenic nonepileptic seizures are mainly caused by emotional and psychological disorders, and the possibility of causing elevated uric acid is also low. Our study also confirmed that serum uric acid levels and elevation percentage were significantly higher in the group with GTCS than in the groups with syncope and PNES. Therefore, serum uric acid levels can be used as an indicator to distinguish transient disturbances in consciousness, especially in GTCS and nonepileptic disturbance of consciousness.

Because there is a sex difference in the normal reference values for uric acid, our study also compared different groups according to sex. The results suggest that serum uric acid levels and elevation percentage in the group with GTCS were significantly higher than those in the groups with syncope and PNES, regardless of sex. The serum uric acid level and elevation percentage in male patients in the group with GTCS were significantly higher than those in female patients. Higher serum uric acid levels in males may be related to a higher baseline. Serum uric acid levels in the group with GTCS were negatively correlated with age, which may be also due to stronger inflammatory response in younger adults. However, no study to date has clearly supported this speculation.

Our follow-up results for some patients suggest that elevated serum uric acid levels in patients with epilepsy is transient. It decreases over time at a relatively fast rate, and returns to a normal level within 3 days in most patients. The reason may be that the related reactions in certain inflammatory signaling pathways inducing seizures come to a halt, thus returning uric acid levels to normal.

Previous studies have also proposed other serum markers to differentiate among epilepsy, syncope, and PNES. Goksu et al. [22] proposed serum creatine kinase (CK) level as an indicator to distinguish GTCS and syncope; however, the elevation percentage of CK level is not especially high in patients with GTCS, leading to low sensitivity of serum CK level as a differential indicator. The level of neuron-specific enolase has also been proposed as an indicator to distinguish syncope and epilepsy [23], with serum lactate level also among the list [24,25]. Our study proposed serum uric acid levels as an indicator to differentiate among GTCS, syncope, and PNES. Moreover, as an item in routine biochemical tests, serum uric acid is more convenient in emergency applications than neuron-specific enolase and lactic acid. Therefore, in clinical practice, especially when a quick identification of the cause of disturbance of consciousness is needed in emergency situations, serum uric acid levels have a certain clinical value for the differentiation of GTCS with syncope and PNES.

There were limitations to the present study. First, the diagnosis of GTCS, syncope, and PNES was not based on synchronous video-EEG with seizures, mainly because there are too few patients who meet the gold standard. Second, the sample size of followed-up patients with GTCS grouped by sex was too small, which may have affected the results and final conclusions.

Our study proposed serum uric acid level as a marker with a high specificity and an acceptable sensitivity to differentiate among GTCS, syncope, and PNES, which has certain value for the rapid diagnosis of patients who experience disturbances in consciousness in emergency situations. However, prospective studies including a larger sample size are needed to confirm the reliability of our conclusion. In addition, closer study of serum uric acid levels at different time points after seizures can contribute to better understanding of the pattern of uric acid levels after onset of the disease, which can further guide and facilitate clinical applications.

Declaration of Competing Interest

The authors have no competing financial interests in relation to the work presented.

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