Epilepsy & Behavior 75 (2017) 13–17

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

# Clinical utility of serum lactate levels for differential diagnosis of generalized tonic–clonic seizures from psychogenic nonepileptic seizures and syncope

Ebru Apaydın Doğan [a,*], Ali Ünal [a], Aslıhan Ünal [b], Çağla Erdoğan [a]

[a] Akdeniz University School of Medicine, Neurology Department, Antalya, Turkey
[b] Akdeniz University School of Medicine, Emergency Department, Antalya, Turkey

ARTICLE INFO

*Article history:*
Received 12 June 2017
Revised 1 July 2017
Accepted 4 July 2017
Available online 12 August 2017

*Keywords:*
Lactate
Generalized tonic clonic seizures
Psychogenic nonepileptic seizures
Syncope

ABSTRACT

*Background:* The differential diagnosis of generalized tonic–clonic seizures (GTCS), psychogenic nonepileptic seizures (PNES), and syncope constitutes a major challenge. Misdiagnosis rates up to 20 to 30% are reported in the literature.
*Purpose:* To assess the clinical utility of serum lactate levels for differentiation of GTCS, PNES, and syncope based on gender differences.
*Methods:* Data from 270 patients were evaluated retrospectively. Only patients ≥18 years old with the final diagnosis of GTCS, PNES, or syncope in their chart were recruited. Serum lactate levels were measured in the first 2 h of the index event.
*Results:* Serum lactate levels in patients with GTCS ($n = 157$) were significantly higher than in the patients with PNES ($n = 25$) ($p < 0.001$) and syncope ($n = 88$) ($p < 0.001$). When compared with the females, serum lactate levels in patients with GTCS were significantly higher in the male subgroup ($p = 0.004$). In male patients the ROC analysis yielded a serum lactate value of 2.43 mmol/l with a sensitivity of 0.85 and a specificity of 0.88 as the optimal cut-off value to distinguish GTCS from other events. The ROC analysis for the AUC yielded a high estimate of 0.94 (95% confidence interval: 0.91–0.98). When a cut-off value of 2.43 mmol/l was chosen for the females, which was an optimal value for male patients, the specificity was 0.85, however, the sensitivity was 0.64.
*Conclusion:* We propose that serum lactate level when measured in the first 2h after the index event has a high clinical utility in the differential diagnosis of GTCS, PNES, and syncope. With concomitant clinical signs and physical examination findings besides neuroimaging and EEG, elevated levels of lactate should be taken into account when evaluating a patient with impaired consciousness. On the other hand, the suggested cut-off value 2.43 mmol/l might not have a discriminative effect between GTCS, PNES, and syncope in female patients. This finding should be verified in a prospectively designed study with a larger patient population.


## 1. Introduction

The differential diagnosis of generalized tonic–clonic seizures (GTCS), psychogenic nonepileptic seizures (PNES), and syncope constitutes a major challenge. Misdiagnosis rates up to 20–30% are reported in the literature [1]. Both PNES and syncope may appear identical to true epileptic seizures and lead to incorrect diagnosis [2]. Electroencephalography (EEG) might be helpful during the diagnostic process. However, patients with epilepsy can have normal EEGs, and patients without epilepsy may show EEG abnormalities [3]. Therefore, clinical findings with a detailed history and EEG combined with a rapid bedside diagnostic test would help minimize the diagnostic pitfalls.

Lactate is being suggested as an important diagnostic laboratory parameter which can easily be measured and provides useful information when incorporated into the appropriate clinical context [4–7]. The use of lactate as a clinical prognostic tool was first suggested in 1964 by Broder and Weil when they observed that a lactate excess of >4 mmol/l was associated with poor outcomes in patients with undifferentiated shock [7].

Although much has been published on the utilization of lactate in a variety of patient populations since that time, there are only a limited number of studies in which serum lactate levels were compared in patients with epileptic seizures, PNES, and syncope. In these studies, effects of gender have not been investigated [8,9]. In our study, we aimed to analyze the clinical utility of serum lactate levels in the differential diagnosis of GTCS, PNES, and syncope with particular interest for the effects of gender.

* Corresponding author.
*E-mail address:* eapaydindogan@yahoo.com (E.A. Doğan).

http://dx.doi.org/10.1016/j.yebeh.2017.07.003
1525-5050/

## 2. Patients and methods

Hospital charts of 22,450 patients who had been admitted to the Emergency Department (ED) of Akdeniz University Faculty of Medicine between September 2016 and March 2017 were analyzed retrospectively.

Strict criteria were used. Only patients aged ≥18 y diagnosed with GTCS, PNES, or syncope and completed final chart data including computed tomography and/or magnetic resonance imaging, EEG, and electrocardiography (ECG) with observed clinical signs and symptoms were recruited. Patients with septic shock and those with alcohol intake and use of metformin were not included. Serum lactate levels were not used either to make or to exclude the diagnosis.

Serum lactate levels were measured immediately (in the first 15 min of admission) at patient arrival in ED. The elapsed time between the index event and hospital admission was less than 2 h in all patients. The cutoff level of serum lactate level was 2.20 mmol/l as determined by the Akdeniz University Hospital. Only the patients with normal serum pH levels were recruited.

### 2.1. Statistical analysis

Statistical analysis was performed using SPSS 18 Software (SPSS Inc., Chicago, IL, USA). The age distribution of the patients was characterized by median and range. The distribution of serum lactate levels was described by median and range. Comparison of serum lactate levels and age between patient groups were made by Mann–Whitney *U* test. A receiver operating characteristic graph, with the *y*-axis representing the serum lactate level's sensitivity (true positive rate) and the *x*-axis representing 1-specificity (false-negative rate), was used to plot the points of sensitivity and specificity for various serum lactate levels. The area under the curve (AUC) quantified the overall diagnostic accuracy of the serum lactate level.

## 3. Results

Two hundred seventy patients who met the inclusion criteria were identified. Of these, 157 patients (91 male, 66 female) had a putative diagnosis of GTCS. Twenty-five patients (13 male, 12 female) presented with PNES, and 88 patients (48 male, 40 female) presented with syncope.

Generalized tonic–clonic seizures, syncope, and PNES were not formally confirmed by simultaneous video-EEG/ECG recordings, but the final diagnosis was based on reports of laymen and the findings of all available diagnostic examinations. Age characteristics and serum lactate levels according to clinical diagnoses are presented in Table 1. Distribution of serum lactate levels in male and female patients are presented in Tables 2 and 3, respectively.

The median serum lactate level in the GTCS group was 3.64 mmol/l (range 0.76–17.16); 133 (84.7%) of these patients had increased serum lactate levels (≥2.2 mmol/l). Contrarily, the median serum lactate level of the other 2 groups (PNES + syncope) was 1.52 mmol/l (range 0.04–5.31 mmol/l). Only 20 (17.7%) of these patients had increased serum lactate levels (≥2.2 mmol/l). Serum lactate levels in patients with GTCS (n = 157) were significantly higher than the patients with PNES (n = 25; $p < 0.001$) and syncope (n = 88; $p < 0.001$). Similar results were obtained when GTCS group was compared with the nonepileptic group (PNES + syncope) (n = 113, $p < 0.001$). There was no significant difference regarding serum lactate levels in patients with syncope and PNES ($p = 0.12$).

When compared with the females, serum lactate levels in patients with GTCS were significantly higher in the male subgroup ($p = 0.004$) (Table 4, Fig. 1). In male patients, the ROC analysis yielded a serum lactate value of 2.43 mmol/l with a sensitivity of 0.85 and a specificity of 0.88 as the optimal cutoff value to distinguish GTCS from other events. The ROC analysis for the AUC yielded a high estimate of 0.94 (95% confidence interval: 0.91–0.98) (Fig. 2). When a serum lactate level of 2.85 mmol/l was chosen as a cutoff value, a higher level of specificity was obtained (0.98), but the sensitivity value decreased to 0.70 in male patients.

The ROC curve analysis in female patients had a lower estimate of AUC which was 0.82 (95% confidence interval: 0.74–0.89). A cutoff value of 2.26 mmol/l had a sensitivity of 0.70 and specificity of 0.79 to distinguish GTCS from other events. When a cutoff value of 2.43 mmol/l was chosen for the females, which was an optimal value for male patients, the specificity was 0.85; however, the sensitivity was 0.64. The ROC curve analysis in all patients (n = 270) yielded a sensitivity of 0.74 and a specificity of 0.88 for the cutoff value of 2.45.

## 4. Discussion

According to the data of our study, we present three major findings (i) when compared to patients with PNES and syncope, serum lactate levels are significantly higher in patients with GTCS; (ii) gender has a definite discriminative effect and male patients with GTCS have significantly higher serum lactate levels when compared to female patients with GTCS; (iii) the cutoff value of 2.43 mmol/l for serum lactate concentration might not be a reliable parameter in female gender considering the differentiation of GTCS, PNES, and syncope as the sensitivity was low.

Our findings are concordant with the recently published data by Matz et al. in which serum lactate concentration of 2.45 mmol/l yielded

**Table 1**
Distribution of age and serum lactate levels in all patient groups.

| Clinical diagnosis | Age median (range), y | Lactate level median (range), mmol/l | Number of Px with elevated lactate levels ≥2.2 mmol/l, (%) |
|---|---|---|---|
| GTCS (n = 157) | 44 (18–92) | 3.64 (0.76–17.16) | 133 (84.7%) |
| PNES (n = 25) | 40 (18–84) | 1.30 (0.23–3.82) | 3 (12.0%) |
| Syncope (n = 88) | 67.5 (18–91) | 1.59 (0.04–5.31) | 17 (19.3%) |
| PNES or syncope (n = 113) | 58 (18–91) | 1.52 (0.04–5.31) | 20 (17.7%) |

GTCS: generalized tonic–clonic seizures, Px: patients, y: years PNES: psychogenic nonepileptic seizures.

**Table 2**
Distribution of age and serum lactate levels according to clinical diagnoses in male patients.

| Clinical diagnosis | Age median (range), y | Lactate level median (range), mmol/l | Number of male Px with elevated lactate levels ≥2.2 mmol/l, (%) |
|---|---|---|---|
| GTCS (n = 91) | 41 (18–86) | 4.12 (0.76–17.16) | 84 (92.3) |
| PNES (n = 13) | 28.0 (18–84) | 1.20 (0.61–2.19) | 0 (0) |
| Syncope (n = 48) | 63 (21–91) | 1.62 (0.34–3.03) | 8 (16.7) |
| PNES or syncope (n = 61) | 58 (18–91) | 1.47 (0.34–3.03) | 8 (13.1) |

GTCS: generalized tonic–clonic, Px: patients, y: years, PNES: psychogenic nonepileptic seizures.

**Table 3**
Distribution of age and serum lactate levels according to clinical diagnoses in female patients.

| Clinical diagnosis | Age median (range), y | Lactate level median (range), mmol/l | Number of male Px with elevated lactate levels ≥2.2 mmol/l, (%) |
|---|---|---|---|
| GTCS (n = 66) | 44 (18–92) | 3.24 (0.94–10.94) | 49 (74.2) |
| PNES (n = 12) | 46.5 (20–72) | 1.60 (0.23–3.82) | 3 (25.0) |
| Syncope (n = 40) | 68 (18–89) | 1.53 (0.04–5.31) | 9 (22.5) |
| Syncope + PNES (n = 52) | 59.5 (18–89) | 1.53 (0.04–5.31) | 12 (23.1) |

GTC: generalized tonic–clonic, Px: patients, y: years, PNES: psychogenic nonepileptic seizures.