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Serum prolactin level and lactate dehydrogenase activity in patients with epileptic and nonepileptic seizures

A cross-sectional study

Murat Yilmaz, MD[a,*], Beliz Oztok Tekten, MD[b]

Abstract

It is important to diagnose epilepsy in a timely and accurate manner, and also to distinguish it from non-epileptic conditions. The present study was aimed at determining postictal serum prolactin levels and lactate dehydrogenase (LDH) activities in patients with new-onset seizure admitted to the emergency department in order to assess whether they could be used in the differentiation of epileptic seizure (ES) from nonepileptic seizure (NES).

Eighty-five patients were included prospectively in this study. Patients were divided into 2 groups with respect to epilepsy diagnosis, and the final groups were comprised of 36 patients with ES and 49 patients with NES. Blood samples were obtained within 1 hour of seizure.

No significant differences between groups were observed in prolactin levels and in the percentage of patients with abnormal prolactin level ($P = .569$ and .239, respectively). The median LDH activity was significantly higher in those with ES compared with those with NES ($P = .031$). The percentage of patients with elevated LDH levels was similar between 2 groups ($P = .286$).

This was the first study to examine LDH activities in terms of its role in differentiation of seizure origin in the postictal period in patients hospitalized with seizure. Our study demonstrated that serum LDH activities within 1 hour after the seizure appear to be increased in patients with ES compared with those with NES, suggesting the potential role of LDH activities as a diagnostic tool in distinction of seizure types. Our study supports the hypothesis that LDH-antagonists may have a role in the management of seizure and epilepsy.

Abbreviations: ATP = adenosine triphosphate, EEG = electroencephalography, ES = epileptic seizure, LDH = lactate dehydrogenase, NES = nonepileptic seizure, PNES = psychogenic non-epileptic seizure.

Keywords: epilepsy, lactate dehydrogenase, lactate dehydrogenase prolactin, seizure

1. Introduction

A seizure is a transient disruption of brain function manifesting with clinical symptoms of excessive, uncontrollable, abnormal, and synchronous discharges of neuronal activity, primarily in the cerebral cortex.[1] Observable features depend on type of seizure, and vary from sudden involuntary abnormal motor activity involving most of the body with temporary loss of consciousness (generalized seizure) to uncontrolled movements involving only some part(s) of the body with varying levels of consciousness (focal seizure), or a slight momentary loss of awareness (absence seizure).[2] An important approach in the management of a patient with a history of seizures is accurate assessment of etiopathogenesis. The most common type of seizure in the adulthood is epilepsy which stands as the common neurological condition worldwide. Epilepsy is classically characterized by recurrent (≥2) unprovoked seizures with an interval of at least 24 hours.[3] In epilepsy, profound changes in the energy homeostasis of the brain can be identified and these may be the cause or result of the epileptic condition.[4] The diagnosis of epilepsy is made clinically, based on patient history and standard neurological examinations. Distinguishing between epileptic and non-epileptic seizures reveals itself to be a challenging task even for experienced clinicians. Clinical characteristics of seizures are instrumental in differentiating non-epileptic seizure (NES) from epileptic seizure (ES), albeit this approach is diagnostic in <70% of cases.[5] A misdiagnosis can cause increased substantial morbidity and healthcare costs and delayed treatment, as well as long-term side effects of drugs due to unnecessary medication use. Therefore, serum parameters that can distinguish ES from NES have been sought in many studies.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

[a] *Department of Neurology, Bolu Abant Izzet Baysal University, Bolu, Turkey,* [b] *Department of Emergency Medicine, Bolu Abant Izzet Baysal University, Bolu, Turkey.*

[*] *Correspondence: Murat Yilmaz, Department of Neurology, Bolu Abant Izzet Baysal University, BAIBU Golkoy Yerleskesi, 14030 Merkez/Bolu, Turkey (e-mail: dryilmazmurat@gmail.com).*

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Prolactin is a polypeptide synthesized and secreted from the pituitary gland and its levels are controlled by the hypothalamus through dopamine. It has been considered as a biomarker in the differential diagnosis of ES from NES, as a result of evidence suggesting the possibility of a relationship between the degree of increased serum prolactin levels and extent of epileptic activity.[6] However, the results of research in this context, as well as the sensitivity of prolactin measurements, are inconclusive and conflicting.

Lactate dehydrogenase (LDH) is a unique enzyme that catalyzes the reversible conversion of lactate to pyruvate, which is released due to all types of tissue, and is associated with common injuries and diseases, including heart failure, renal diseases, autoimmune diseases, and cancers.[7] LDH is a essential for energy metabolism of neuronal cells through astrocyte-neuron lactate shuttle.[8] Under the conditions with high energy requirements of brain, such as tumors and seizure, astrocyte-derived lactate can be used as a main energy source for neurons.[4] Recent studies have reported that epileptiform activity and seizures can be suppressed by inhibiting LDH activity, thus supporting LDH as a molecular target for the development of new antiepileptic drugs.[9] However, few studies have examined the relationship between serum LDH activities and different seizure types, and their results remain unclear.

The aim of this study was to determine the value of postictal serum prolactin level and LDH activity in the differentiation of ES from NES among patients with new-onset seizure who were admitted to the emergency department.

2. Methods

This prospective cross-sectional study was conducted between February 2020 and December 2020 in the Emergency and Neurology Departments of Bolu Abant Izzet Baysal University Hospital, Bolu, Turkey. Patients admitted to the emergency department suspected to have new-onset seizures presenting within 1 hour of ictus were included in the study. Patients with a history of epilepsy, pregnancy, endocrinological and renal comorbidity, metabolic disorders (including hypoglycemia and hypocalcemia), autoimmune diseases, mental impairment, alcohol abuse, chronic inflammatory conditions, acute or chronic infections, muscle injuries, and patients who had received any medication before being admitted to our emergency department were excluded from the study 12 patients were excluded from the study with regard to exclusion criteria. The final study group was comprised of 85 patients who had applied with new-onset seizure. All research procedures were evaluated and accepted by the Clinical Research Ethics Committee of Bolu Abant Izzet Baysal University and were conducted in agreement with the ethical standards specified in the Declaration of Helsinki. Written and verbal informed consent was obtained from each individual prior to blood withdrawal for this study.

After admitting to the emergency department, patients underwent a clinical examination including neurological examination, performed by the same researcher. Clinical and demographic characteristics, including age, sex, type of seizure, previous medication(s), and comorbidities were recorded. Chest X-ray, electrocardiography, and electroencephalography (EEG) were ordered. Radiological cerebral imaging was performed with computerized tomography and magnetic resonance imaging to assess neurological conditions. Radiological results of all patients were evaluated by the same researcher under the highest possible magnification. Patients were followed up prospectively after the clinical evaluation subsequent to new-onset seizure. The study group was divided into 2 groups; those who were diagnosed with epilepsy (the ES group) and those who were not (the NES group). Thirty-six patients were diagnosed with epilepsy and 49 patients were defined to have NES. The diagnosis of epilepsy was based on the decision of the neurologist according to the history, observed clinical condition, and the examination of the patient during and after the seizure.

Blood samples were drawn from the antecubital vein within 1 hour after seizures. Serum prolactin levels were measured with the electrochemiluminescent immunoassay technique on the automated Architect i2000 SR analyzer with standard kits according to the manufacturer's instructions (Abbott Laboratories, IL). The intra-assay and interassay coefficient of variability of prolactin measurement were <5%. Interpretation of the prolactin level was based on the manufacturer's recommendations, as follows: normal range for men was 3.46 to 19.4 μg/L, and normal range for non-pregnant women was 5.18 to 26.53 μg/L. Serum LDH activity and C-reactive protein levels were determined using the automated Architect c4000 analyzer employing a photometric method (Abbott Laboratories, IL). A C-reactive protein (CRP) value of >5 mg/L was considered as an abnormal result. Expected normal ranges for LDH were 125 to 220 IU/L. Both serum CK-MB levels and Troponin I levels were measured with highly specific monoclonal antibodies via a sensitive electrochemiluminescent immunoassay method using the Architect i2000SR auto-analyzer (Abbott Laboratories, IL). Values up to 26 ng/L were considered normal for troponin I. The normal range of the CK-MB test was 0 to 24 IU/L in both sexes.

2.1. Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL). For the normality check, histograms and Q–Q plots were used. Data are given as mean ± standard deviation or median (1st quartile–3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed with the independent samples *t* test. Non-normally distributed variables were analyzed with the Mann–Whitney *U* test. Categorical variables were analyzed with Pearson Chi-square tests or Fisher exact tests, depending on expected/actual group counts. $P < .05$ values were accepted to show statistically significant results.

3. Results

A total of 85 patients with new-onset seizure, 36 with epileptic seizure, and 49 with non-epileptic seizure, were enrolled in the study. The mean age of patients in the ES and NES groups were 50.42 ± 21.93 years and 50.61 ± 20.67 years, respectively. No significant differences were found between the 2 groups with regards to age and sex ($P = .967$ and $P = .337$, respectively). In the ES group, 29 patients (80.56%) had generalized seizures, 2 patients (5.56%) presented with focal seizures, and 5 patients (13.89%) had absence seizure (syncope/blackout). In the NES group, 27 patients (55.10%) were found to have absence seizure (syncope/blackout), 15 patients (30.61%) presented with generalized seizures, and 7 patients (14.29%) had focal seizures. None of the participants had status epilepticus. In the ES group, 19 patients, including 7 patients with non-specific ischemic gliosis

Table 1

Clinical characteristics of patients.

	Non-epileptic seizure (n = 49)	Epileptic seizure (n = 36)	*P*-value
Age (n = 85)	50.61 ± 20.67	50.42 ± 21.93	.967
Gender (n = 85)			
Female	24 (48.98%)	13 (36.11%)	.337
Male	25 (51.02%)	23 (63.89%)	
Type of seizure (n = 85)			
Focal	7 (14.29%)	2 (5.56%)	**<.001**
Generalized	15 (30.61%)	29 (80.56%)	
Absence (syncope/blackout)	27 (55.10%)	5 (13.89%)	
Status	0 (0.00%)	0 (0.00%)	
Abnormal CT imaging (n = 64)	21 (58.33%)	19 (67.86%)	.603
Acute ischemic stroke	2 (5.56%)	1 (3.57%)	
Hematoma	0 (0.00%)	0 (0.00%)	
Encephalomalacia	6 (16.67%)	7 (25.00%)	
Non-specific ischemic gliosis	11 (30.56%)	7 (25.00%)	
Tumoral mass	0 (0.00%)	1 (3.57%)	
Contusion	0 (0.00%)	0 (0.00%)	
Other space occupying lesion	2 (5.56%)	3 (10.71%)	
Abnormal MRI (n = 48)	14 (58.33%)	14 (58.33%)	1.000
Acute ischemic stroke	3 (12.50%)	2 (8.33%)	
Hematoma	0 (0.00%)	1 (4.17%)	
Encephalomalacia	3 (12.50%)	5 (20.83%)	
Non-specific ischemic gliosis	7 (29.17%)	5 (20.83%)	
Tumoral mass	0 (0.00%)	0 (0.00%)	
Contusion	0 (0.00%)	0 (0.00%)	
Other space occupying lesion	1 (4.17%)	1 (4.17%)	

Data are given as mean ± standard deviation or median (1st quartile–3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables.
Bold values represent the *p* values lower than 0.05.

Table 2

Biochemical characteristics of patients.

	Non-epileptic seizure (n = 49)	Epileptic seizure (n = 36)	*P*-value
CK-MB (n = 32), IU/L	16.8 (12.9–20.8)	28.6 (18.6–43.3)	**.025**
Normal	14 (82.35%)	7 (46.67%)	.080
High	3 (17.65%)	8 (53.33%)	
Troponin I (n = 55), ng/L	4 (1.1–11.9)	4.9 (1.85–17.15)	.806
Normal	30 (85.71%)	18 (90.00%)	1.000
High	5 (14.29%)	2 (10.00%)	
Prolactin (n = 85), μg/L	21.02 (12.63–40.18)	17.08 (10.61–36.42)	.569
Low	0 (0.00%)	2 (5.56%)	.239
Normal	23 (46.94%)	17 (47.22%)	
High	26 (53.06%)	17 (47.22%)	
LDH (n = 54), IU/L	236 (217–322)	336 (259–405)	**.031**
Normal	9 (29.03%)	3 (13.04%)	.286
High	22 (70.97%)	20 (86.96%)	
CRP (n = 85), mg/L	1.4 (0.1–5)	3.5 (0.1–11.4)	.192
Normal	37 (75.51%)	21 (58.33%)	.148
High	12 (24.49%)	15 (41.67%)	

Data are given as median (1st quartile–3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables.
CK-MB = creatine kinase-myocardial band, CRP = C-reactive protein, LDH = lactate dehydrogenase.
Bold values represent the *p* values lower than 0.05.

and 7 patients with encephalomalacia, had abnormal CT results, while 21 patients in the NES group showed abnormal findings. MRI studies showed abnormality in 14 patients in the ES group and also 14 patients in the non-epileptic group. Clinical features of patients are shown in Table 1.

The median prolactin levels were found to be similar in the epileptic group (17.08 [10.61–36.42] μg/L) and in the non-epileptic group (21.02 [12.63–40.18] μg/L) ($P = .569$). The number of patients with increased prolactin were 26 (53.06%) in the NES group and 17 (47.22%) in the ES group ($P = .239$).

The median LDH activities were significantly higher in patients diagnosed with epileptic seizure (336 [259–405] IU/L) compared with patients with non-epileptic seizure (236 [217–322] IU/L) ($P = .031$). The percentage of patients with elevated LDH levels was similar between 2 groups ($P = .286$).

The median CK-MB values were significantly higher in the ES group (28.6 [18.6–43.3] IU/L vs 16.8 [12.9–20.8] IU/L, $P = .025$). Median Troponin I levels were 4.9 (1.85–17.15) ng/L in patients with epilepsy and 4 (1.1–11.9) ng/L in the NES group ($P = .806$). No significant differences were observed between the 2 groups in terms of CRP levels ($P = .192$). The biochemical features of our group of new-onset seizure patients are shown in Table 2.

4. Discussion

The current study aimed to evaluate postictal serum biochemical parameters in patients with new-onset seizures to ascertain whether they could be used to distinguish patients with ES or NES. Our data demonstrated that serum LDH activity was significantly increased in patients with ES compared with those with NES, suggesting the use of discriminating epileptic seizures from non-epileptic seizures in the postictal period. We found no significant differences in prolactin levels and in the percentage of patients with elevated prolactin levels when the ES and NES groups were compared. The 2 groups were also similar with regards to CRP and Troponin I levels.

Epilepsy is a global health care challenge and an estimated 5 million people are diagnosed with epilepsy each year.[10] It is estimated that approximately four-fifths of epilepsy patients live in low- and middle-income countries which may be more affected by the physical, mental, social, and financial burden imposed by epilepsy.[10] Many clinicians have to face the challenge of differentiating seizures of epileptic and non-epileptic origin in their daily clinical practice; however, this distinction requires clinical awareness, experience, and sufficient time for evaluation, which may be limited in the emergency department where the majority of such cases are initially admitted. Therefore, the lack of an objective diagnostic tool that can reliably support diagnosis remains as a problem for swift decision-making in such patients. Currently, clinical examination and observation at the time of seizure are accepted as the gold standards for differentiating seizure etiology. Video-EEG monitoring is also an important diagnostic technique, but this approach requires long-term hospitalization of the patient, typically days or weeks, rendering it unsuitable for many patients. In addition, this technique is expensive and is effective if a seizure can be captured while the patient is being monitored.[11] EEG is widely used to aid in the diagnosis of epilepsy, which detects the electrical activity of the brain using electrodes attached to the scalp. It has several limitations including poor spatial resolution, difficult to identify the source of the signals, and also limited sensitivity.[12] Moreover, EEG cannot unquestionably exclude epilepsy from psychogenic non-epileptic seizure (PNES) and vasovagal syncope.[11] Serum biochemical markers are cheap and available in

most hospitals, and have been considered to be useful in distinguishing ES from NES in the postictal period.

Prolactin levels have been tried and tested in discriminating seizures, and has shown some promising and some controversial results. Singh and Jana showed higher prolactin levels in 15 patients with generalized seizures (28.6 ng/mL) compared with 8 patients with pseudoseizures (10.4 ng/mL) and 6 healthy controls (9.8 ng/mL), when measured within 15 to 20 minutes of the seizure.[13] Willert et al[14] found a greater degree of increase in postictal serum prolactin levels (measured at 10, 20, 30 minutes, 1 and 6 hours) in patients with epileptic seizures compared with patients with PNES. In contrast to these studies, Shukla et al[15] revealed similar prolactin levels and also similar percentages of patients with abnormal prolactin levels in their comparison of PNES and true complex partial seizures with or without secondary generalization, when measured within 15 to 20 minutes of seizure. Javali et al[16] demonstrated in 100 patients with new-onset seizures that serum prolactin levels measured within 1 hour were elevated in all subjects with generalized tonic-clonic seizures and 75% of patients with focal seizures. They also showed that none of the participants with PNES had an increase in PRL levels. We found similar prolactin levels measured within 1 hour after the seizure in our ES and NES groups, and the percentage of patients with abnormal prolactin levels were similar in both groups. Our study indicates that postictal serum levels of prolactin may not be used as a diagnostic tool to distinguish ES from NES when measured at 1 hour after seizure. The lack of difference may be due to the timing of blood sampling, but a previous study by Pritchard et al[17] showed increased prolactin levels at 15, 30, 45, and 60 minutes in 6 epileptic patients compared with 6 pseudoepileptic seizures. It is evident that the result of their study is hampered by limited power. In another study, Tharyan et al[18] demonstrated significant post-seizure elevation in serum prolactin levels among epileptic patients (including generalized tonic clonic seizures and complex partial seizures). Their findings revealed a peak at 20 minutes and a fall towards baseline by 1 hour, which might explain the absence of significant differences in our group of patients. Abnormal electrical discharges of a seizure in epileptic patients may stimulate hypothalamo-pituitary axis either directly (through specific neurotransmitter alterations) or indirectly through the release of other substances, and these effects can cause increased release of prolactin in a time-dependent manner. Since the half-life of prolactin is about 20 minutes, the demonstrated trend of increase within 20 minutes after the event and decrease at 1 hour postictal, dictates that blood samples should be collected within 15 to 20 minutes after the seizure.[19]

LDH is a unique catalyzing enzyme the interconversion of lactate back to pyruvate in tricarboxylic acid cycle that produces adenosine triphosphate (ATP) into mitochondria. Lactate is transported from astrocytes to neurons via the astrocyte-neuron lactate shuttle, a major metabolic pathway for supplying energy to neurons.[20] LDH is essential for the astrocyte-neuron lactate shuttle in the brain.[9] Elevated lactate formation through LDH activities typically occurs in overactive tissues when oxygen availability is limited, such as tumor cells and seizures. Recently, it was reported that the inhibition of LDH reduced the excitability of neurons in a seizure model in mice, suggesting a role for LDH-inhibitors among antiepileptic medications.[9] The same researchers also showed in another mice seizure model that seizures increased LDH expression and activity in astrocytes, which further exacerbated seizures.[21] Thus, we aimed to investigate the role of serum LDH levels in epilepsy and also in the differentiation of seizure type in humans. This was the first study to examine LDH activities with respect to its role in the discrimination of seizure type during the postictal period in patients hospitalized with seizure. We demonstrated increased postictal LDH levels in epileptic patients compared with seizure patients without epilepsy within 1 hour after the seizure. Our findings indicate that postictal serum LDH levels could increase in the sera of seizure patients, suggesting the use of postictal serum LDH in the differentiation of seizure origin. This increase may be related with the result of overuse of LDH to provide lactate to neurons due to increased energy demands during seizure. ATP-sensitive potassium channels may close through increased ATP with LDH activity during seizures, leading to increased neuronal hyperpolarization and discharge. The differences between groups also indirectly support the hypothesis that LDH could be a promising target for development of new anti-seizure medication. The use of LDH-antagonists drugs in seizure may lead the accumulation of pyruvate and may limit the availability of NAD^+ as well as may allow full oxidation of pyruvate to CO_2 and H_2O. With LDH antagonists in seizure, the intracellular ATP concentration may decrease and potassium channels may be opened, resulting in hyperpolarization of the neuronal cell membrane with potassium ion efflux and a decrease in neuronal excitation. LDH antagonists may also mimic effects of glucose restriction diet. Further studies with larger sample size and temporal blood sampling during the postictal period are required to confirm our results.

The first limitation of our study was that we were unable to determine baseline prolactin levels and LDH activities in our patient group. This would have been important to observe the precise changes in the 2 groups. Secondly, we did not perform our study with blood sampling at different time intervals. Therefore, we could not observe the time-bound changes in the measured parameters, which may have been crucial for particularly prolactin level and LDH activity. Although our sample size was large when compared with the majority of prior studies on this topic, there is a need for greater studies with the inclusion of patients with different genetic characteristics and other features that could alter baseline levels of measured parameters. Finally, prolactin levels can be affected by conditions such as prolactinomas, primary hypothyroidism, and certain medications including tricyclic antidepressants and dopamine antagonists.[19] We could not exclude these factors in our study.

4.1. Conclusion

This was the first study to examine LDH activities in terms of its role in differentiation of seizure origin in the postictal period in patients hospitalized with seizure. Our study demonstrated that serum LDH activities within 1 hour after the seizure appear to be increased in patients with ES compared with those with NES, suggesting the potential role of LDH activities as a diagnostic tool in distinction of seizure types. Our study supports the hypothesis that LDH-antagonists may have a role in the management of seizure and epilepsy. Further studies with larger samples and sequential measurements during the postictal period are required to confirm our results.

Author contributions

Conceptualization: Murat Yilmaz, Beliz Oztok Tekten.

Data curation: Beliz Oztok Tekten.
Formal analysis: Beliz Oztok Tekten.
Investigation: Beliz Oztok Tekten.
Methodology: Murat Yilmaz, Beliz Oztok Tekten.
Project administration: Murat Yilmaz.
Resources: Murat Yilmaz.
Software: Murat Yilmaz, Beliz Oztok Tekten.
Supervision: Murat Yilmaz.
Visualization: Murat Yilmaz.
Writing – original draft: Murat Yilmaz, Beliz Oztok Tekten.
Writing – review & editing: Murat Yilmaz, Beliz Oztok Tekten.

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