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Lactate as a diagnostic marker in transient loss of consciousness

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ABSTRACT

Purpose: The diagnostic classification of disorders of consciousness is often challenging, particularly the distinction between epileptic and non-epileptic seizures. The aim of the study was to examine serum lactate as a diagnostic marker of transient loss of consciousness.
Method: Serum lactate levels in blood samples drawn within 2 h of the event were compared retrospectively between patients with generalized tonic-clonic seizures ($n = 195$) and patients with other seizures (syncopes [$n = 52$], psychogenic non-epileptic seizures [$n = 17$], and complex focal seizures [$n = 37$]), respectively.
Results: Serum lactate in patients with generalized tonic-clonic seizures was significantly ($p < 0.001$, Mann–Whitney-*U* test) increased in comparison to other forms of seizure incidences. The area under the ROC-curve was 0.94 (95% CI 0.91–0.96). For a cut-off concentration of 2.45 mmol/l, the sensitivity was 0.88 and the specificity 0.87.
Conclusions: Serum lactate levels in the acute diagnosis were an excellent biomarker for the discrimination of generalized seizures from psychogenic non-epileptic and syncopal events, corroborating its importance for the standard work-up of acute disturbances of consciousness.

1. Introduction

Revealing the etiology of transient impairments of consciousness is an interdisciplinary task, which often remains unsuccessful despite a wide range of available diagnostic tests. From a neurological perspective it is important to discriminate epileptic and non-epileptic events. Syncopes and psychogenic non-epileptic seizures in particular can be difficult to distinguish from epileptic seizures.

It is usually possible to correctly categorize an event on the basis of the patient's medical history. In a large number of cases the cause remains unclear, for the most part due to the diversified clinical presentation of epileptic seizures, ranging from a subtle loss of awareness lasting only few seconds, to complex movement disorders and loss of consciousness lasting for considerable time spans [1].

Clinical symptoms such as drowsiness, enuresis or a bite mark on the tongue may hint at an epileptic seizure yet may also occur in non-epileptic events [2,3]. This leads to persisting uncertainty even in cases that were observed by a third party, and even more so in unobserved events.

The results of diagnostic examinations such as a computer tomography or an electroencephalogram (EEG) can support, yet rarely prove, the diagnosis of an epileptic seizure. An EEG helps the diagnosis in the rare event of recording an epileptic seizure during the event, but frequently is unspecific between seizures. Neuroimaging is only supportive to clarify the etiology of a previously diagnosed epileptic seizure.

Useful for the correct categorization of an event, however, are the laboratory parameters creatine kinase and prolactin. Both parameters are increased after epileptic tonic-clonic seizures [4,5].

A diagnostic marker which so far gained little attention is serum lactate concentration measured right upon admission. Orringer et al. [6] observed that generalized tonic-clonic seizures led to increased serum lactate levels within 2 h after the seizure, the reason being increased anaerobic glucose metabolism during the short hypoxia experienced by muscle cells during a tonic-clonic seizure [7].

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To date, only a single study was conducted comparing serum lactate levels of patients who experienced a tonic-clonic seizure with patients with consciousness disorders of unknown etiology. In that study, patients with tonic-clonic seizures had significantly elevated levels of serum lactate, in contrast to the group of patients with unclear consciousness disorders. Notably, the study did not discriminate the cause of the impairment of consciousness as syncopal, psychogenic non-epileptic or another non-epileptic nature [8].

The serum lactate level has been established as an important diagnostic and prognostic marker in other settings since the early 1960s, when Broder and Weil demonstrated that elevated serum lactate following various forms of shock correlated with adverse outcome. Specifically, the authors observed a worsening of the patients' outcome when the serum lactate level rose above 4 mmol/ml [9].

There is no generally accepted cut-off value that would represent a serum lactate increase. Usually, a serum lactate concentration above 2.0–2.5 mmol/l is regarded as elevated. Levels around 4–5 mmol/l are universally accepted as being elevated. Such serum lactate concentrations in conjunction with a blood pH value of $\leq$7.35 constitute a lactic acidosis [10–12].

Lactate is produced by many cells of the human body, mostly by muscle cells. Lactate is mainly metabolized in the liver [13]. Lactic acidosis typically occurs when cells are short of oxygen, forcing them to metabolize glucose anaerobically, which leads to lactate formation. Therefore, elevated lactate is indicative of tissue hypoxia as well as hypoperfusion, which occurs amongst other incidences during shock [14–16].

If lactic acidosis occurs without substantial hypoxia, it is usually characterized by either increased production or reduced elimination, caused by biguanid therapy in diabetics or various liver diseases [17–20].

The aim of this study was to assess the diagnostic value of serum lactate concentration as a marker in the diagnosis of consciousness disorders with unknown etiology, with a focus on the differential diagnosis of epileptic seizures compared to other forms of consciousness disorders. Serum lactate levels were compared in patients with generalized tonic-clonic seizures, complex partial seizures, psychogenic non-epileptic seizures and syncopes, respectively.

2. Patients and methods

In a retrospective analysis, 1101 patients were identified who had been admitted to the emergency room of the University Hospital of the RWTH Aachen between June 2012 and June 2014 with the diagnosis of an epileptic seizure, a psychogenic non-epileptic seizure, or a syncope. Of these, 301 patients (27.3%) had a confirmed diagnosis and their serum lactate levels were measured within 2 h after the event.

The patients were categorized in four groups depending on the kind of event: 195 patients were classified as having suffered a generalized tonic-clonic seizure, 37 patients presented with complex partial seizures, 17 patients as having a psychogenic non-epileptic seizure, and 52 had experienced a syncope. Of the 52 with a syncope, 6 had a convulsive syncope. All patients with a psychogenic non-epileptic seizure had a clinical manifestation in the form of a pseudoconvulsive attack.

Patients were only included in the study if the diagnosis was certain or very likely according to the following criteria: observed tonic-clonic seizures in patients with known epilepsy, observed seizures exhibiting typical clinical signs and symptoms, and the diagnosis had been entered in the final discharge report. For patients without reliable anamnestic report, we relied on information from paramedic reports, from documentation in the emergency room, and discharge reports. Serum lactate levels were not used to confirm the diagnosis.

The second challenge was to ascertain the time that had elapsed between the event and the measurement of serum lactate. In some cases the time of the event was documented in the paramedic report. In other cases the time of the initial alert to the paramedics, or else the time at which vital signs were first checked, were used to estimate the time of the event. The serum lactate levels were measured at patient arrival in the emergency room. The cut-off concentration constituting a lactate increase, as by the standards of the laboratory of the Aachen University Hospital, was 2.2 mmol/l.

2.1. Statistical analysis

Statistical analysis was performed using SPSS 22 Software (SPSS Inc., Chicago, IL, USA). The age distribution in the patient pool was characterized by mean and standard deviation. The distribution of serum lactate levels was described by median and range. Serum lactate levels between patient groups were compared with a Mann–Whitney-*U* test. The effectiveness of serum lactate levels in the different groups was ascertained by a ROC (Receiver Operating Characteristics) analysis [21], by plotting the true positive rate (TPR) against the false positive rate (FPR) for various cut-off settings. The optimal cut-off value was determined via the Youden index [22]. The Area under the Curve (AUC) was considered a measure for the discriminatory power of serum lactate level.

3. Results

195 patients were diagnosed as having had a generalized tonic-clonic seizure (69 female, 126 male, age (mean, standard deviation, range) 51.16 $\pm$ 21.01, 19–94), 37 presented with a complex partial seizure (25 female, 15 male, age 68, 23 $\pm$ 19.41, 18–97), 52 patients experienced a syncope (31 female, 21 male, age 58.48 $\pm$ 23.07, 19–91) and 17 patients presented with a psychogenic non-epileptic seizure (8 female, 9 male, age 37.11 $\pm$ 15.26, 20–58). The median serum lactate level in the generalized tonic-clonic group was 4.7 mmol/l (range 1.0–20.0 mmol/l, see Table 1, Fig. 1). The total number of patients in this group with increased serum lactate levels (>2.2 mmol/l) was 183 (93.8%). This is in stark contrast to the serum

Table 1
Medians and ranges of serum lactate levels and number of elevated lactate levels in each group.

Seizure type	Number of patients	Serum lactate level median (mmol/l)	Range (mmol/l)	Number of elevated lactate levels ($\geq$2.2 mmol/l)
GTCS	195	4.7	1.0–20.0	183 (93.8%)
CPS	37	1.8	0.7–4.9	11 (29.7%)
PS	17	1.4	0.6–2.9	3 (17.6%)
Syncope	52	1.7	0.5–3.9	10 (19.2%)
Not GTCS	106	1.7	0.5–4.9	24 (22.6%)
Syncope + PS	69	1.6	0.5–3.9	13 (18.8%)

GTCS, generalized tonic clonic seizure; CPS, complex partial seizure; PS, psychogenic non-epileptic seizure; not GTCS = syncope + PS + CPS.

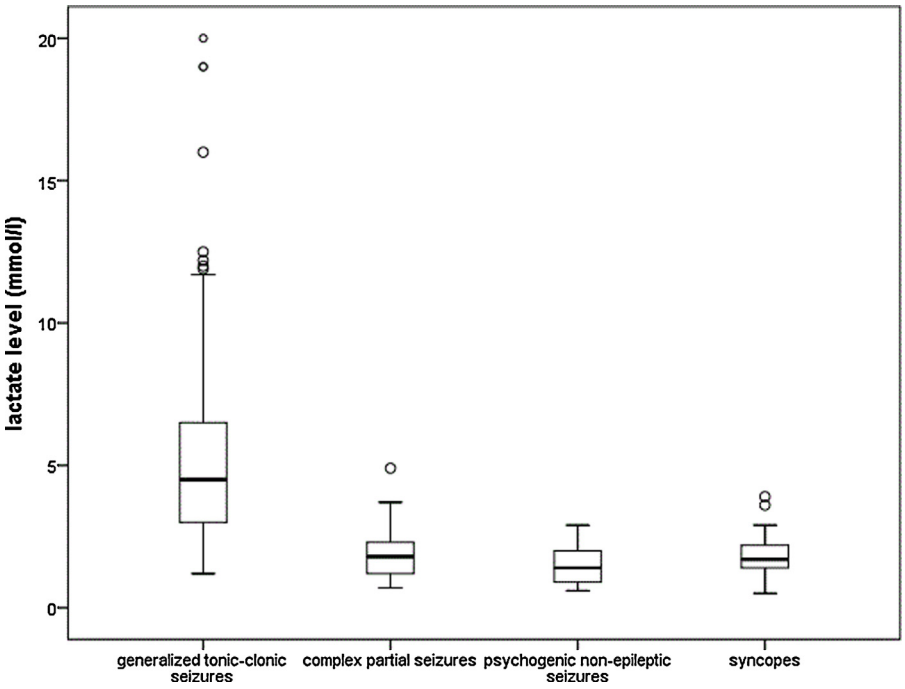

Fig. 1. Distribution of serum lactate levels (mmol/l) in the four patient groups separately. The median is indicated by a thick crossbar. Compared to the three other patient groups, serum lactate levels in the group with generalized tonic-clonic seizures were significantly increased, with a median of 4.7 mmol/l (range 1.0–20.0 mmol/l).

lactate levels of the other 3 groups which was 1.7 mmol/l (range 0.5–4.9 mmol/l). The serum lactate levels of patients with non-epileptic events had a median of 1.6 mmol/l (range 0.5–3.9 mmol/l). In the group with syncopes, 6 experienced a convulsive syncope; out of these, two showed elevated serum lactate levels ($n = 6$, median 1.8 mmol/l, range 0.9–3.6 mmol/l).

Serum lactate levels in patients with generalized tonic-clonic seizures ($n = 195$) were significantly higher than those in the group with all other seizure types combined (not GTCS: syncopes, psychogenic non-epileptic seizures, complex partial seizures, $n = 106$, $p < 0.001$). This held also true when comparing the generalized tonic-clonic group to the non-epileptic group (syncopes, psychogenic non-epileptic seizures, $n = 69$, $p < 0.001$).

The ROC analysis yielded a serum lactate value of 2.45 mmol/l with a sensitivity of 0.88 and a specificity of 0.87 (Table 2, Fig. 2) as the optimal cut-off value to distinguish generalized tonic-clonic seizures from other events. If the goal was best specificity, a serum lactate level of 3.15 mmol/l was determined as the optimal cut-off, with a specificity of 0.96 and a sensitivity of 0.75. The ROC analysis for the AUC yielded a high estimate of 0.94 (95% confidence interval (CI): 0.91–0.96).

A comparison of the generalized tonic-clonic group with the non-epileptic group yielded a similar AUC (GTCS vs. syncope + psychogenic non-epileptic seizures: 0.94, 95% CI 0.92–0.97), with a cut-off of 2.45 mmol/l resulting in a specificity and sensitivity of 0.88, each.

A Mann–Whitney-*U* test revealed no significant differences between the complex partial group ($n = 37$) and the non-epileptic group ($n = 69$).

4. Discussion

This study shows that patients who just suffered a generalized tonic-clonic seizure exhibit highly elevated serum lactate concentrations within 2 h after the event compared to patients who suffered other forms of impairment of consciousness. With an AUC of 0.94 in the ROC analysis, serum lactate concentrations prove a very good prognostic indicator for a generalized tonic-clonic seizure. A serum lactate concentration of 2.45 mmol/l yielded a sensitivity of 0.88 and a specificity of 0.87 for a generalized tonic-clonic seizure as cause of the impairment of consciousness. When emphasis was on increasing specificity, a serum lactate level of 3.15 mmol/l resulted in a specificity of 0.96 for a generalized tonic-clonic seizure causal of a consciousness disorder.

The present study thus yielded a similar result to the work of Hazouard [8] that compared serum lactate levels from patients with generalized tonic-clonic seizures with serum lactate levels from patients with consciousness disorders of unknown etiology. A serum lactate concentration of 2.5 mmol/l had a sensitivity of 0.73 and a specificity of 0.97 for generalized tonic-clonic seizures.

Consciousness disorders of unknown etiology often represent an interdisciplinary diagnostic challenge. Since they can be a symptom of a serious condition which might need immediate treatment, a quick and targeted diagnostic approach is crucial. As we have shown in this study, serum lactate concentration can serve as a diagnostic marker to categorize events of unclear consciousness disorders. Highest relevance is assumed for the discrimination of generalized tonic-clonic seizure from non-epileptic events such as syncopes and psychogenic non-epileptic

Table 2
Distribution of serum lactate levels in each group at a cut-off value of 2.45 mmol/l.

	GTCS	CPS	PS	Syncope	Not GTCS	Syncope+PS
Serum lactate (≥2.45 mmol/l)	172 (88.2%)	6 (16.2%)	2 (11.8%)	6 (11.5%)	14 (13.2%)	8 (11.6%)
Serum lactate (<2.45 mmol/l)	23 (11.8%)	31 (83.8%)	15 (88.2%)	46 (88.5%)	92 (86.8%)	61 (88.4%)

GTCS, generalized tonic clonic seizure; CPS, complex partial seizure; PS, psychogenic non-epileptic seizure; not GTCS = syncope + CPS + PS.

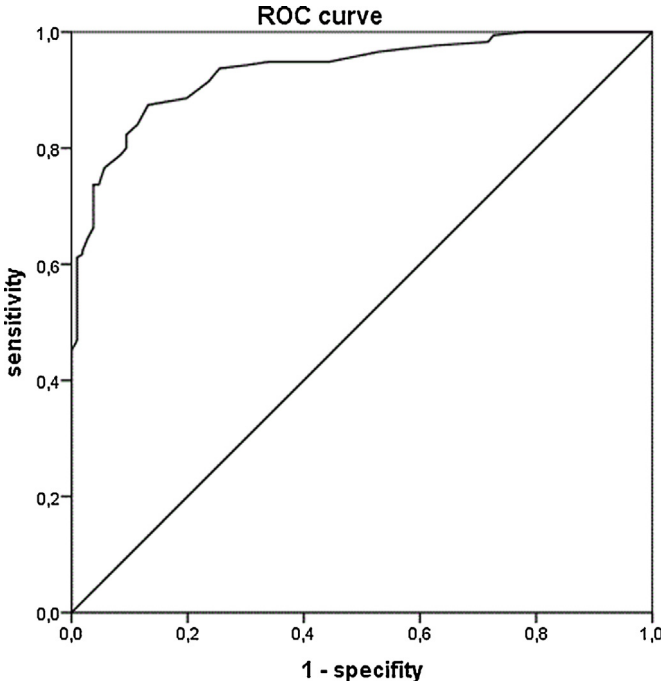

Fig. 2. ROC analysis for serum lactate level as a marker for the presence of generalized tonic-clonic seizure. The analysis for the AUC yielded a high estimate of 0.94 (95% confidence interval (CI): 0.91–0.96).

seizures. Our data show a highly significant difference in serum lactate levels between patients with a generalized tonic-clonic seizure and other forms of consciousness disorders. The majority of patients who underwent a generalized tonic-clonic seizure had markedly elevated serum lactate concentrations, while this held true only in very few patients who presented with syncopes or with psychogenic non-epileptic seizures. In these cases, elevation of lactate concentration was less pronounced than in the cases presenting with a generalized tonic-clonic seizure. We were unable to pinpoint the reasons for elevated lactate concentrations in patients without generalized tonic-clonic seizures. It remains unclear whether lactate levels are elevated in patients presenting with convulsive syncopes. Our study included six cases of convulsive syncopes, two of which had elevated serum lactate levels. The number of patients in this group is however too small to test if convulsive syncopes also raise serum lactate levels.

Regarding the patients with psychogenic non-epileptic seizures, it should be mentioned that all patients experienced a pseudoconvulsive and not a pseudosyncopal event. It is therefore unclear, albeit likely, whether the patients with psychogenic non-epileptic seizures and clinical manifestation in form of pseudosyncopal event also have normal serum lactate levels.

Serum lactate levels can be elevated for various reasons, e.g. sepsis, tumors, alcoholism and certain medications [23–26]. This should be taken into account when using them as a diagnostic marker. Another trivial cause is applying the tourniquet for too long before venipuncture, allowing lactate to build up in the drawn blood sample.

Serum lactate levels turn out less useful in distinguishing partial complex seizures from non-epileptic events. Some of the patients with complex partial seizures had elevated lactate levels. In most of these cases the reasons for this elevation seemed to be unrelated to the seizure itself. Possible causes include occurrence of a generalized tonic-clonic seizure prior to the complex partial one. There even might be yet unknown mechanisms of serum lactate increase in epileptic seizures other than excessive muscle activity.

Serum lactate differs from the two more established diagnostic markers, serum creatine kinase and prolactin in some aspects. Prolactin may be increased after a generalized tonic-clonic seizure, but also be increased after a complex partial seizure. A non-elevated prolactin level by itself is insufficient to exclude the possibility of an epileptic seizure. The diagnostic value of prolactin lies mainly in the discrimination between epileptic seizures and psychogenic non-epileptic seizures, in which the prolactin levels usually are normal [27,28].

Prolactin is rather unsuitable to distinguish between epileptic seizures and syncopes because increased prolactin levels were detected even after syncopes [29,30]. By contrast, serum lactate levels are helpful to distinguish a generalized tonic-clonic seizure from a syncope.

Prolactin and serum lactate are both increased early after a seizure. Significantly elevated prolactin levels are often found up to an hour after the event, with a peak after about 15–25 min [31]. A caveat for both parameters is that in daily routine, the time of the event to the first blood sample in the emergency department is eventually sometimes too long for both parameters so that the serum levels are already normalized again.

The creatine kinase as another relevant diagnostic marker is similar to the serum lactate suitable for distinguishing generalized tonic-clonic seizures from syncopes and psychogenic non-epileptic seizures [32,33].

The time interval to increase and the duration of elevated levels differ between the two markers. A significant increase in creatine kinase is often detected within the first two days. Sometimes the maximum level of creatine kinase activity is found on the third or fourth day after the event [34]. Libman et al. found improved sensitivity of the creatine kinase when blood sampling was done at least three hours after the event [35]. Due to this delayed increase, creatine kinase is probably inferior to serum lactate as early diagnostic marker. Another drawback of the creatine kinase marker is that syncopes often lead to falls with traumatic muscle injury, and a trauma-associated increase may result in incorrect suspicion of an epileptic seizure.

In conclusion, serum lactate level can be a very good diagnostic tool to categorize unclear consciousness disorders, particularly to differentiate generalized tonic-clonic seizures from syncopes and psychogenic non-epileptic seizures. If a patient is admitted with unclear consciousness disorder and shows pronounced elevation of serum lactate, there is a high likelihood of a generalized tonic-clonic seizure; therefore further investigations should include a computer tomography and an electroencephalogram. On the other hand, when serum lactate is not markedly elevated and tonic-clonic stigmata like a tongue bite mark or a postictal confusion are also absent, the patient should be admitted to further cardiologic examinations.

The rapid normalization of the serum lactate level after a generalized tonic-clonic seizure limits its value as diagnostic marker to only a few hours after the event. The time-dependent sensitivity and specificity of serum lactate levels needs to be curtailed in further studies. It would also be useful to compare serum lactate with the two other laboratory parameters creatine kinase and prolactin in a prospective study.

Conflicts of interest

None.

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