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Review

The role of postictal laboratory blood analyses in the diagnosis and prognosis of seizures

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ABSTRACT

Background: Epileptic seizures (ES) lead to alterations in the blood laboratory values and reflect changes in different organ systems. Here, we review the diagnostic and prognostic value of various blood laboratory values within the context of epilepsy.
Methods: Narrative review and literature search on PubMed using the term, "seizure" and various laboratory values.
Results: Laboratory markers can help clinicians determine whether an unwitnessed event was more likely to be epileptic or non-epileptic. Prolactin testing helps differentiate ES from psychogenic non-epileptic seizures (PNES) in adults and adolescents, and is associated with high specificity and moderate sensitivity. Elevations in the creatine kinase (CK) levels are common after generalized tonic-clonic seizures (GTCS) and display high specificity and moderate sensitivity. Metabolic markers such as ammonia and lactate may have diagnostic potential for postictal blood tests.
Analyzing blood postictally is important for identifying the cause of the symptomatic seizures due to endocrine, metabolic, toxic or infectious etiologies.
Finally, laboratory analyses are used for identifying patients who are at risk for developing rare, threatening complications such as rhabdomyolysis, acute renal failure (ARF) or cardiomyopathy.
Conclusions: Presently, no postictal laboratory values can definitively prove or rule out the diagnosis of an epileptic seizure. For seizures with unknown causes, simple blood tests can be a valuable aid for quickly defining the etiology, particularly with certain metabolic and toxic encephalopathies. For this reason, CK, electrolytes, creatinine, liver and renal function tests should be measured on at least one occasion. Further research is needed in order to identify new biomarkers that improve the diagnosis and prognosis of seizures and seizure-related complications.

1. Introduction

The physiologic consequences of an epileptic seizure depend on the type, length and intensity of the seizure, as well as the patient's preexisting condition.

Seizures lead to distinctive metabolic changes. Maximal neuronal excitation incites the neuroendocrine system to secrete hormones such as catecholamines and prolactin. Whole body muscle contractions and the release of catecholamines increase cerebral, muscular and cardiac oxygen demands, while impaired breathing impedes compensatory mechanisms in order to satisfy this demand. Strained tissues release metabolites such as lactate, ammonia and urea, while irritated skeletal muscles leak creatine kinase and myoglobin. Afterwards, an inflammatory reaction with cytokine release and leukocytosis occurs.

The metabolic changes listed above are most pronounced in generalized tonic clonic seizures (GTCS) and status epilepticus (SE), but even partial seizures, especially those that are accompanied by

Abbreviations: ACS, acute coronary syndrome; ADH, antidiuretic hormone; ARF, acute renal failure; AVP, arginine vasopressin; BNP, brain natriuretic peptide; CAD, coronary artery disease; CK, creatine kinase; CPS, complex partial seizures; CSF, cerebrospinal fluid; cTNI, cardiac troponin I; cTNT, cardiac troponin T; ct-proAVP, C-terminal pro arginine vasopressin; ECG, electrocardiogram; EEG, electroencephalogram; ES, epileptic seizures; ER, emergency room; FC, febrile convulsions; GH, growth hormone (somatropine); GTCS, generalized tonic clonic seizure; ICU, intensive care unit; LH, luteinizing hormone; LOC, loss of consciousness; FSH, follicle stimulating hormone; NSE, neuron specific enolase; NT-pro-BNP, N-terminal pro brain natriuretic peptide; PNES, psychogenic non-epileptic seizures; PRL, prolactin; SE, status epilepticus; SPS, simple partial seizures; SUDEP, sudden unexpected death in epilepsy; TIA, transient ischemic attack; TSE, thyroid stimulating hormone; VPA, valproic acid; V-EEG, video-EEG.

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autonomic symptoms such as periictal tachycardia, conduction block, asystole or respiratory disturbances, can lead to physiological and metabolic changes that can be analyzed with laboratory testing [1].

Our narrative review on the value of postictal blood testing is based on the following three questions:

1.) Which blood tests aid in the differential diagnosis of epileptic versus non epileptic seizures?
2.) Which blood tests can help establish the etiology? A postictal blood test will not only demonstrate the consequences of seizures, but also the preexisting alterations that may be the actual cause of the seizures (such as electrolyte disorders and metabolic encephalopathies).
3.) Which blood tests help predict potential seizure complications? While most seizures are benign, some can be complicated by rhabdomyolysis, acute renal failure and cardiomyopathies. These can be detected early on with

Table 1
Overview of studies analyzing PRL as an aid in differentiating ES from PNES after Chen and colleagues, 2005. Prolactin elevations occur in ~60% of GTCS, ~46.1% of CPS and ~6.7% of PNES.

Author, Year	Groups	Age	Setting	Time	Elevated PRL	Comments
Wilert, 2004 [19]	44 patients: 32 ES 12 PNES	18–62	V-EEG, prospective	10, 20, 30 min, 1, 6, 12, 24 h	M > 16.5 ng/ml, F > 23 ng/ml 20 min: ES 28/32 (87.5%) PNES 4/12 (33%)	Sensitivity 87.5% Specificity 66.7%
Shah, 2001 [20]	89 patients with multiple events: 36 GTCS 56 CPS 27 SPS 55 PNES	Not provided	V-EEG, prospective	Immediately after event	2x baseline level GTCS 17/36 (47.2) CPS 19/56 (33.9%) SPS 3/27 (11.1%) PNES 1/55 (1.8%)	GTCS sensitivity 47.2% CPS sensitivity 33.9% SPS 11.1% Specificity 98.2%
Alving, 1998 [21]	58 patients: 38 ES patients 20 PNES patients 4 SPS 20 CPS 16 GTCS 20 PNES	13–68	Video- or mobile EEG monitoring, prospective	15 min and 2 h after event	2x baseline level: All ES: 69% CPS 61% GTCS: 93% PNES 20.4% exact numbers not provided	All ES sensitivity 69% CPS sensitivity 61% GTCS sensitivity 93% specificity 74%
Ehsan, 1996 [31]	50 patients: 13 GTCS 17CPS 6 SPS 14 PNES	6–61	V-EEG, prospective	15 min and 1 h after event	2x baseline level: GTCS 10/13 (76.9%) CPS 15/17 (88.2%) SPS 0/6 (0%) PNES 2/14 (14.3%)	CPS sensitivity 88.2% GTCS sensitivity 76.9% SPS sensitivity 0% Specificity 85.7%
Fisher, 1991 [22]	20 patients: 9 GTCS 7CPS 4 PNES	>18	V-EEG, prospective	10–20 min after event	>36 ng/ml GTCS 5/9 (55.6%) CPS 1/7(14.3%) PNES 0/4 (0%)	GTCS sensitivity 55.6% CPS sensitivity 14,3% Specificity 100%
Rao, 1989 [2]	11 patients: 2 GTCS 4 CPS 5 PNES	13–47	V-EEG, prospective	Immediately, every 15 min for 2 h	2x baseline level GTCS 2/2 (100%) CPS 3/4 (75%) PNES 0/5 (0%)	GTCS sensitivity 100% CPS sensitivity 75% Specificity 100%
Wroe, 1989 [23]	33 patients: 8 GTCS 11 CPS 4 Absence 10 PNES	15–73	V-EEG, prospective	10 min after event	>45 ng/ml GTCS 6/8 (65.6%) CPS 5/11 (Absence 0/4 (0%) PNES 0/10 (0%)	GTCS sensitivity 65.6% CPS sensitivity 45.5% Absence sensitivity 0% Specificity 100%
Laxer, 1985 [24]	70 patients, multiple events 64 ES 21 PNES	9–54	V-EEG, prospective	Within 20 min after event and at 24 h	25 ng/ml ES 40/61 (65.6%) PNES 1/18 (5.6%)	Sensitivity 65.6% Specificity 94.4%
Pritchard, 1985 [25]	12 patients: 1 GTCS 5 CPS 6 PNES	Not provided	V-EEG, prospective	15 min after event	2x baseline level GTCS 1/1 (100%) CPS 5/5 (100%) PNES 0/6 (0%)	GTCS sensitivity 100% CPS sensitivity 100% Specificity 100%
Oxley, 1981 [18]	18 patients, multiple events 6 GTCS 4 CPS 10 PNES	Not provided	Mobile EEG, prospective	Within 20 min after event	>36 ng/ml GTCS 4/6 (75%) CPS 0/4 (0%) PNES 1/10 (10%)	GTCS sensitivity 75% CPS sensitivity 0% Specificity 90%
Chen, 2005 [4]	Pooled analysis of the studies mentioned above	GTCS: sensitivity 60% (48.9–71.1). specificity 95.9% (91.4–100) CPS: sensitivity 46.1% (36.5–55.7). specificity 96.3 (92.7–99.9) All ES: sensitivity 52.6% (47–58.2). specificity 92.8 (89.9–95.7)				

laboratory tests which, in turn, allows for a timely therapeutic intervention.

A systematic review which includes all the laboratory values available after a seizure occurs is beyond the scope of a single article. Hence, when systematic reviews are available, they are referenced accordingly. Laboratory changes in status epilepticus (SE) or electroconvulsive therapy (ECT) are not covered in this review, but will be mentioned if there is interest. Generally, a status epilepticus tends to exaggerate the laboratory changes found in a single seizure. We focused on blood findings and did not include tests involving other body liquids such as cerebrospinal fluid, urine or saliva. Furthermore, we want to stress that some postictal complications such as delirium, psychosis or injuries only rely on the clinical evaluation and examination and not on laboratory tests. Thus, these entities were not included in our review.

2. Methods

We searched the PubMed database for articles in English containing the search word "seizure" and the laboratory values mentioned below.

Five types of articles were included. They are listed in order of highest to lowest attributed validity:

1.) Prospective studies performed after seizures were recorded during video-EEG monitoring. These types of studies are advantageous as the seizure type, duration, associated physiological parameters, as well as the time to laboratory testing can be precisely determined. The etiology is known and confounding factors such as substance abuse, injuries and preexisting conditions are checked. However, the small number of patients normally found in such studies is a disadvantage.
2.) Prospective studies conducted after seizures were witnessed in emergency rooms (ERs) and hospitals.
3.) Prospective studies conducted on patients who were admitted to ERs and hospitals postictally.
4.) Retrospective and case control studies conducted on patients who were admitted to ERs and hospitals postictally. These types of studies tend to have the largest patient numbers and the most heterogeneous population. A further limitation is that the seizure type is not definitively identified. A certain number of events that are misdiagnosed as ES must be expected in these studies.
5.) Case reports.

3. Results

3.1. Which blood tests aid in the differential diagnosis of epileptic versus non epileptic seizures?

3.1.1. Hormone changes and their role in the differential diagnosis

ES impact the hypothalamic-pituitary axis and sympathetic nervous system via connections between the limbic structures and hypothalamus. GTCS and CPS may lead to an increase in prolactin (PRL), growth hormone (GH), adrenocorticotropin (ACTH), thyreotropin (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH), as well as arginin vasopressin (AVP) [2].

3.1.1.1. Prolactin: the classic marker used in the differential diagnosis. In the 1970s and 1980s, PRL levels were first measured after ES and PNES based on the hypothesis that seizure activity which arises from the mesial temporal lobe can alter the hypothalamic control of PRL release. [3–6]. Since then, PRL has become one of the most extensively studied biomarkers for determining seizure disorders. PRL rises after GTCS in ~60% of the cases, after electroconvulsive seizures, after alcohol withdrawal seizures and, to a lesser degree, following CPS (~45%), but rarely after SPS and PNES [7–18]. PRL measurements require caution, since PRL physiology harbors a number of limitations towards establishing normal values. PRL levels depend on age, gender and circadian rhythm, e.g. surging by as much as 50–100% upon awakening. Furthermore, PRL is influenced by common medications and conditions such as pregnancy, nursing and even psychological stress [4]. Finally, when compared to healthy controls, patients with epilepsy tend to have alterations in the interictal PRL [4].

Serum PRL peaks rapidly (within 10–20 min after a seizure) and returns to baseline within two to six hours [4]. If the PRL measurements are used to distinguish CPS or GTCS from PNES, blood samples should be drawn 10–20 min after the event. Sensitivity reaches 46.1% for CPS and 60% for GTCS, with a specificity of 95.9–96.3% in an analysis of pooled data [2,4,19–29] and illustrated in Table 1. An elevation of PRL within the 10–20 min timeframe indicates an ES, while normal PRL levels neither exclude an ES nor prove a PNES [4,30]. Since it is difficult to quickly obtain these measurements for outpatients, capillary blood samples in filter paper were investigated but did not achieve widespread clinical use [22,31]. Because the above mentioned factors cause PRL to fluctuate, most authors count a threefold increase of PRL as significant when compared to the individual baseline, while others established different thresholds for men and women [6].

In the differential diagnosis between syncope and seizures, PRL is of little use since syncope itself may lead to PRL elevations in 60–80% of patients. In this regard, the data obtained from children are more conflicting than for adults [32–38].

Repetitive seizures may lead to repetitive, and even increasing, PRL peaks. However, in status epilepticus, the PRL levels may rise only initially and then return to normal levels despite ongoing ictal activity due to PRL storage depletion [4,6,39–41].

Earlier video-EEG-monitoring studies indicated that seizures with a temporal lobe origin lead to PRL elevations more often than seizures originating in the frontal lobe. This finding was not replicated in 60 patients with temporal lobe onset CPS and 20 patients with frontal lobe onset CPS as determined by invasive video EEG monitoring [42–44].

Most authors concur that the PRL level rises after febrile or afebrile convulsions in children [45,46]. Others found elevations only after an epileptic seizure occurred but not after a febrile seizure [47].

In neonates, the available data is limited. Baseline PRL levels are highly variable and depend on the degree of the underlying encephalopathy. Two studies detected an elevation of PRL after an ES, while another demonstrated elevated, interictal baseline PRL in infants with ES, but without relevant postictal elevations. PRL measurements in neonates are generally not used to detect seizures [4,48–50].

PRL cannot be used post mortem to determine if a deceased individual had a seizure before dying. It is possible that death occurs before PRL is released from the pituitary gland [51,52].

3.1.1.2. Arginine vasopressin (AVP) and copeptin: potential new biomarkers in the differential diagnosis. AVP (a.k.a. ADH) [53], is an important regulator of the water and sodium homeostasis. Simultaneously, AVP is part of the endocrine stress response and is increased after ES [16,39].

Copeptin (ct-proAVP) is the C-terminus of pre-pro-AVP and secreted together with it. In contrast to AVP, which is very unstable, copeptin has a long serum half-life. It can be measured reliably for days at room temperature and even weeks in frozen samples.

One study compared the interictal blood values of copeptin and endothelin, but found no difference between patients with syncope, epilepsy and 22 controls. Periictal investigations in ES, PNES or syncope are still lacking [54].

A study on copeptin and prolactin was conducted on 161 children that presented to the ER with FC (n = 83), fever without convulsions (n = 69) or ES without fever (GTCS n = 7, CPS n = 2). Children with ES and with FC had higher levels of both copeptin and prolactin. The diagnostic accuracy for differentiating between controls and FC was higher for copeptin with a sensitivity of 67.5% and a specificity of 88.4% [55].

More information on copeptin is provided in Section 3.3.

3.1.1.3. Other pituitary hormones. ACTH and cortisol elevations occur as a reaction to various stressful events including ES, PNES, syncope and other stressors [25,29,37,56], even though they may be accentuated in GTCS and CPS [17,57–59]. Elevations of GH were reported in some studies on adults and children [17,60], but not

Table 2
Overview and pooled analysis of studies with CK. CK elevations occur in ~45% of all GTCS. CK elevations can be used as an aid in the differential diagnosis of GTCS versus syncope and PNES with low sensitivity but high specificity.

	Author, Year	Groups	Age	Setting	Time	Elevated CK	Comments
GTCS only	Glotzner, 1979 [73]	17 GTCS patients	22–74	ER prospective	1 d through 7 d	14/17 (82.4%) with elevated CK	Day 3: 82.4% CK elevations
	Chesson, 1983 [62]	25 GTCS patients	23–88	ER prospective	1 h through 7 d	21/25 (84%) with elevated CK	84% CK elevations.
	Lahat,1989 [66]	52 FC patients	0.4–5	ER prospective	1 h and 24 h	4/52 at 1 h (7.6%) 18/52 at 24 h (34.6%)	1 h: 7,6% elevations 24 h: 34.6% elevations
	Yanagawa 2007 [71]	15 GTCS patients	7–81	ER prospective	Admission	6/15 (40%) with elevated CK	40% CK elevations (secondary parameter besides NH3)
	Hung, 2011 [80]	30 GTCS patients	>18	ER prospective	Admission	7/30 (23%) with elevated CK	23% CK elevations (secondary parameter besides NH3)
	Sieweke 2012 [70]	741 GTCS patients	17–89	ER retrospective	Admission and stay	303 (40.1%)	40.1% CK elevations. (secondary parameter besides cTNI)
	Our own, yet unpublished data	207 GTCS patients	13–88	ER retrospective	Admission and stay	122/207 (58.9%)	58.9% elevations. Rhabdomyolysis with >50x upper reference in 1.8%.
GTCS vs. PNES	Wyllie, 1985 [72]	12 GTCS patients 41 GTC seizures 15 CPS/SPS patients 147 CP/SP seizures 6 PNE patients 55 PNE seizures	5–47	V-EEG prospective	Daily for 1 week	6/12 GTCS patients (50%) 6/42 GTC seizures (14.3%) 0 of all SPS/CPS 0 of all PNES	Sensitivity 14.6% Specificity 100%
	Willert 2004 [19]	32 ES 12 PNES 16 CTRL	18–62	V-EEG prospective	10 min – 24 h after seizure	ES: 6/32 (18.75%) PNES: 0/12	Sensitivity 19% Specificity 100% after 24h
	Holtkamp, 2006 [65]	8 SE 8 PNES	18–77	ER retrospective	Within 24h	SE: 7/8 (87.5%) PNES: 1/8 (12.5%)	Sensitivity 87.5% Specificity 87.5%
Syncope/ PNES	Petramfar, 2009 [69]	20 GTCS 20 PNES 22 VVS 20 control	adult	ER prospective	12–15 h after admission	GTCS: 15/20 (75%) PNES: 3/20 (15%) VVS: 3/22 (13,6%)	Sensitivity 75% Specificity 85.5%
GTCS vs. syncope	Libman, 1991 [67]	42 ES patients 54 sync patients	>16	ER retrospective	Same day	GTCS: 18/42 (42.9%) sync: 1/54 (1.85%)	Sensitivity 80% Specificity 94% (after 3 h)
	Neufeld 1997 [68]	16 GTCS patients 17 syncope patients	adult	ER prospective	On admission and next day	GTCS adm: 4/16 (25%) GTCS d2: 9/16 (56.2%) sync adm.: 1/17 (5.9%) sync d2: 2/17 (11.8%) >15 U/l rise in GTCS: 11/16 (68.75%) >15 U/l rise in sync: 1/17 (5.9%)	>1.5x elevation admission: Sensitivity 12%, Specificity 94% >1.5x elevation day 2: Sensitivity 25%, Specificity 100% >15 U/l rise: Sensitivity 69%, Specificity 94%.
	Goksu, 2009 [64]	26 GTCS patients 37 sync patients	>16	ER prospective	Admission and 4h	On admission GTCS: 3/26 (11.5%) Syncope: 3/37 (8.1%) After 4 h: GTCS 9/26 (34.6%) Syncope 4/37 (10.8%)	Sensitivity 34.6% Specificity 89.2% After 4 h

Pooled analysis of Wyllie, Willert, Holtkamp, Petramfar (95% confidence interval):
$P < 0.0001$ Sensitivity 47.2% (35.3–59.35), Specificity 91.3% (79.2–97.6), PPV 89.5 (75.-97), NPV 52.5%. (41–63.8).
Pooled analysis of Libman, Neufeld, Petramfar, Goksu calculated with Fishers exact test (95% confidence interval):
$P < 0.0001$. Sensitivity 49% (39.1–59.35), Specificity 92.3% (86.3–96.25), PPV 83.6 (71.9–91.85), NPV 69.7%. (61.9–76.1).
Pooled percentage of CK elevations (all studies above): 45.1%

replicated in others [15,17,60]. Both cortisol and GH levels can be elevated after syncope [33].

Ghrelin and nesfatin-1 are hormonal regulators of hunger and satisfaction. Interictal alterations have been found in epilepsy. One study demonstrated postictal elevations of nesfatin-1 in 34 patients with GTCS, but none in PNES. Ghrelin levels were decreased for one hour after a GTCS. Sensitivity, specificity or predictive values were not provided [61].

3.1.2. Muscle enzymes in the differential diagnosis: creatine kinase (CK) and myoglobin

CK catalyzes the phosphorylation of creatine and ADP to creatinine phosphate and has the highest expression in energy consuming organs such as muscle, heart and brain.

CK rises during the first 1–12 h and peaks after 24–72 h after about 45% of GTCS (Table 2) [7,19,62–72]. CK elevations are unlikely to occur in absence seizures, SPS and CPS [62,72,73], but are found in ~35% of FC after 24 h [66]. Despite significant differences between physiological and seizure-mediated muscle contractions [74], the mechanism causing muscle damage after GTCS is thought to be similar to that of exertional muscle damage: leakage from muscles under high tension and hypoxemia [72].

A recent review specifically examined studies that distinguished PNES from ES [75]. The sensitivity of elevated CK levels in this setting ranged from 14.6 to 87.5%, the specificity from 85 to 100%. PNES that are associated with vigorous motor activity are not associated with CK elevations [65,72]. Some authors, however, have questioned the use of CK measurements in the differential diagnosis of ES versus PNES due to its low sensitivity [19].

Comparisons between GTCS and syncope show that the CK elevations reportedly achieve a sensitivity of 12–75% and a specificity of 85.5–100% [64,67–69]. The specificity increases if sequential samples are collected, especially since syncope can lead to at least mild CK elevations in up to 11%, possibly related to falls [64,68]. Even if CK levels remain within the normal range, an increase of >15 U/l within 24–48 h can be observed in two-thirds of GTCS. There are no data available that specifically compare convulsive syncope to GTCS.

In addition to CK, one study investigated myoglobin levels at admission and 4 h after syncope or GTCS. While CK elevations differentiated between the two, myoglobin did not [64].

In summary, a transitory increase of CK helps distinguish GTCS from syncope or PNES, but is not useful in ruling out GTCS or other types of ES.

3.1.3. Metabolites that help to distinguish epileptic from non-epileptic seizures

3.1.3.1. Ammonia: an emerging marker in the differential diagnosis. Ammonia (NH_3) is an end product of amino acid and purine catabolism. If the hepatic capacity to metabolize ammonia is exceeded, serum NH_3 levels rise and can lead to encephalopathy. NH_3 is used in the diagnosis of hepatic and valproic acid (VPA) encephalopathies, as well as inherited metabolic disorders. Asymptomatic elevations of NH_3 are common in patients of all age groups who are treated with VPA [76]. Increasingly, ammonia has evolved and is now a biomarker for GTCS.

A retrospective ER study found NH_3 elevations in 17/17 GTCS patients (aged 7–81 years), with a spontaneous NH_3 decline the next day [71].

A prospective ER study compared 31 ES patients to 51 patients who displayed other reasons for impaired consciousness. Hyperammonemia on arrival was found in 61.3% of the ES group and none of the controls (other than hepatic encephalopathy). This would

Table 3
Overview of studies investigating elevations of NH3 after GTCS and other causes for loss of consciousness (LOC).

Author, Year	Groups	Age	Setting	Time	Elevated NH3	Comments
Hung, 2011 [80]	121 ES 102 GTCS 13 focal seizures 12 SE 28 alcohol related	>18	ER, prospective	Arrival	GTCS: 76.5% Focal: 30.8% SE: 66.7% Alcohol related: 96.4%	Highest proportion of NH3 elevations in alcohol related GTCS
Liu, 2010 [77]	31 ES (CPS/GTCS) 51 LOC other cause, (not intubated), hepatic encephalopathy	>18	ER, prospective	Arrival and after 1–3 h	NH3 elevation on arrival: ES: 19/31 (61.3%) LOC: 10/51 (19.6%) All LOC patients with NH3 elevation had liver cirrhosis Transient NH3 elevation ES: 17/31 (54.8%) LOC: 0/51 (0%)	NH3 elevation on arrival* Sensitivity: 61.3% Specificity: 80.4% Transient NH3 elevation* Sensitivity: 54.8% Specificity: 100%
Nakamura, 2013 [79]	44 idiopathic GTCS 8 vascular GTCS (15 SE)	>15	ER, retrospective	Arrival	All GTCS: 22/52 (42.3%). Proportions in subgroups not given	High NH3 was associated with acidosis.
Tomita, 2011 [81]	207 convulsive LOC ("mostly" GTCS). 86 LOC of other causes	>16	ER, retrospective	Arrival	Proportions not given	NH3 elevation on arrival (cut-off-value: 65 μg/dl) Sensitivity: 53% Specificity: 90%
Yanagawa, 2007 [71]	17 GTCS	7–81	ER, retrospective	Arrival	17/17 (100%)	High NH3 was not associated with acidosis or CK.
Albadareen, 2016 [83]	13 GTCS 8 focal ES 9 PNES	>18	Video EEG monitoring, prospective	Baseline, 60 min & 24 h after event	Elevation percentages not provided. GTCS: median NH3 doubled Focal ES/PNES: no change in median NH3	Cutoff ≥80 μmol/L Sensitivity: 53.9% Specificity: 100%
Sato, 2016 [181]	379 convulsive seizures	>15	ER, retrospective	Arrival	183/379 (48.2%)	Cutoff ≥50 μmol/L Sensitivity: 48.2% High NH3 was associated with male sex, acidosis, lactate and longer seizures.

Pooled analysis of Hung, Liu, Nakamura, Yanagawa and Sato: elevated NH3 on arrival in the ER occurs in ~54.6% of GTCS.
* Not given in article, calculated by applying Fisher's exact test, $p < 0.001$.

correspond to a sensitivity of 61.3% and a specificity of 80.4%. NH_3 in ES spontaneously returned to baseline levels within 24 h, while it persisted in liver patients [77]. "Transient hyperammonemia in impaired consciousness" had a specificity of 100% and a sensitivity of 54.8%. In a follow-up study, postictal hyperammonemia in 17 GTCS patients was associated with prolonged impairment of consciousness [78].

A retrospective ER study reported transient hyperammonemia in 42.3% of GTCS patients due to genetic (n = 44) or vascular (n = 8) epilepsy to be associated with acidosis. Erythrocytes were discussed as an alternative source of NH_3 release in acidemic conditions [79].

A prospective ER study on 121 patients that excluded patients with cirrhosis or who were taking VPA found that GTCS were associated with transient hyperammonemia lasting 3–8 h in 76.5%, non-convulsive seizures in 21.2%. Male gender, alcohol withdrawal and SE were associated with higher NH_3 levels, as were decreased bicarbonate, elevated CK, creatinine, diabetes and hypertension. NH_3 levels did not predict death, ICU admission or repeated seizures. The authors proposed NH_3 as a new biomarker to fill the time gap between PRL and CK, since PRL is of value only within 20 min postictally, while CK lags behind with a peak 24–48 h after the seizure [80].

A similar ER study on 293 patients with disturbances of consciousness found NH_3 levels to be twice as high in the convulsion group (n = 207) than in the control group (n = 86). With an NH_3 cutoff of 65 μg/ml, sensitivity was 53% and specificity was 90%, with an odds ratio of 14.8 to discriminate convulsions from other causes of impaired consciousness [81].

Another retrospective ER study on 379 patients with convulsive ES found NH_3 elevations in 48.2% of cases [82]. Male sex, prolonged seizures, elevated lactate and acidemia were associated with the NH_3 elevations.

In a recent video-EEG-monitoring trial, the median NH_3 level in 13 patients doubled after GTCS, but remained unchanged after PNES (n = 9) and focal ES (n = 8). An ammonia level of ≥80 μmol/L could correctly classify 80% of the patients (sensitivity 53.9%, specificity 100%) [83].

These data suggest that measurements of NH_3 levels following assumed GTCS may be helpful in the differential diagnosis, e.g. if a GTCS was not observed or is unclear. Table 3 presents an overview.

3.1.3.2. Lactate may become increasingly important in the differential diagnostic process. Excess lactate from muscle tissue is a common finding during the first 1–2 h after a GTCS, but can last longer in SE [84–89]. It can be aggravated by respiratory acidosis due to airway or breathing impairment. Two studies investigated the use of lactate in the differential diagnosis of GTCS versus other causes of transient loss of consciousness. A prospective ER study on 78 patients (22 GTCS, 34 unconscious due to other causes, 22 with epilepsy but admitted for other reasons) found lactate to be 97% specific and 73% sensitive [90]. A large, retrospective ER study on 301 patients (195 GTCS, 37 CPS, 17 PNES, 52 syncope) found lactate levels of >2.45 mmol/l to distinguish GTCS from CPS, syncope and PNES with a sensitivity of 88% and a specificity of 87% [91].

3.1.3.3. Uric acid is not helpful in the differential diagnosis. One study of uric acid in 53 patients with ES and 42 patients with non-epileptic events (14 syncope, 10 TIA, 7 tetanic, 7 hypoglycemic, 4 psychogenic) found increases both in ES and PNES [29]. For more information on uric acid, see Section 3.3.

3.1.4. The cerebral stress markers NSE and S100B are of little value in the differential diagnosis

3.1.4.1. Neuron specific enolase (NSE) has marginal clinical value in everyday epileptology. NSE is the dominant enolase-isoenzyme of neuronal and neuroendocrine tissues. It is used as a prognostic marker after hypoxic and traumatic brain injuries [92–94], and as a tumor marker for small cell lung and neuroendocrine cancer.

After earlier reports found NSE to be elevated in SE [95–97], various studies have investigated NSE in serum and CSF after seizures. Some authors found consistent NSE elevations in serum after single seizures, especially GTCS and CPS [98,99]. In one study, NSE measurements discriminated ES from syncope with a sensitivity of 58% and specificity of 91% [100]. Other authors identified NSE elevations only in about one-third of seizure patients [19,101]. The different study results and interpretations can, in part, be explained by the seizure type and seizure origin, since temporal lobe seizures seemed to increase serum NSE levels more often than extratemporal seizures [102].

In FC, NSE does not increase [103–106]. Additionally, no NSE elevations were found in the severe pediatric seizure syndromes that are associated with brain tissue damage such as West syndrome [107].

3.1.4.2. Protein S100-B is of very limited clinical value in the differential diagnostic process. Protein S100-B is a calcium-binding protein found in astroglia, melanocytes, adipocytes and chondrocytes. It can be measured in urine, serum and CSF to detect severe brain damage such as in rapidly progressive dementias and posthypoxic or posttraumatic states. Elevations due to extracerebral sources can be found in shock, polytrauma and melanoma, where it presents as a tumor progression marker [94]. In epilepsy, initial reports of rising serum S100-B in CSF measured during implantation of foramen ovale electrodes, close to the site of seizure onset [108] were not replicated in controlled, prospective studies of seizures which measured S100-B in serum [101,109,110] or CSF [66]. Further study results were conflicting, as some authors reported no abnormalities in focal or generalized epilepsy [111], whereas others found significant changes in the case of temporal lobe epilepsy, which even correlated with seizure activity and cognitive deficits [112]. In certain clinical situations, interictal serum levels may be useful in differentiating benign diseases from those having a more dangerous course. For instance, serum S100-B was reportedly normal in FC and parasomnias, but increased in children with intractable epilepsy. An acute, severe differential diagnosis of febrile seizures, such as acute encephalopathy with biphasic seizures and late reduced diffusion, (a rare, immunologically-mediated childhood syndrome), is accompanied by S100-B elevations [113–117]. Currently, protein S100-B does not play a routine role in detecting seizures or predicting complications, but may be useful in specific circumstances. More information on protein S100 can be found in Section 3.3.6.

Currently, neither NSE nor protein S100 is routinely used after seizures.

3.1.5. Cardiac markers do not help discern ES from syncope

A study that systematically assessed NT-pro-BNP after seizures in 18–60 year-old patients without prior heart disease who were admitted to the ER <24 h after a transient loss of consciousness, showed no difference between 12 syncope- and 15 ES-patients. The authors did not regard NT-pro-BNP as a suitable marker in distinguishing syncope from ES [118]. More information on cardiac markers is provided in Section 3.3.2.

3.2. Which blood tests help in establishing the etiology of epileptic seizures?

Postictal blood samples may not only provide clues to the differential diagnosis, but also hint towards the etiology of a seizure. In the case of acute, symptomatic seizures due to underlying endocrine, metabolic and electrolyte disorders as well as infections and intoxications, rapid detection is crucial and may be life-saving.

3.2.1. Endocrine disorders as a cause of seizures

Severe thyrotoxicosis, myxedema, hypoparathyroidism (hypocalcemia), diabetes mellitus (hypo/hyperglycemia) and pheochromocytoma (hypertensive crisis) may lead to encephalopathies and seizures [119,120].

3.2.2. Metabolic disturbances as a cause of seizures

Changes in the balance of ions and glucose and the resulting disruptions in neuronal membrane potential and cellular energy metabolism contribute to the initiation, evolution and cessation of epileptic seizures, which in turn lead to systemic, metabolic changes. Many studies that examined systemic changes of electrolytes and glucose were conducted in the first half of the 20th century. The goals were to improve the pathophysiologic understanding and to find a path towards the prediction and treatment of seizures. Historical reviews with more than 200 referenced articles are available [89,121]. In summary, severe aberrations in the metabolic panel facilitate the onset of epileptic seizures and are usually not secondary to a preceding seizure [120].

3.2.2.1. Hypo- and hyperglycemic seizures. Hypoglycemic seizures mostly occur in severe hypoglycemia (<50 mg/dl/2.8 mmol/l) [120,122–124]. Hyperglycemia >400 mg/dl (22.2 mmol/l), especially non-ketotic hyperosmolar states, may cause focal and generalized seizures. The definition of neonatal hypoglycemia remains somewhat controversial [125]. Thresholds for intervention include glucose levels which measure <30 mg/dl (1.7 mmol/l) in the first 2 h and <45 mg/dl (2.5 mmol/l) thereafter.

3.2.2.2. Seizures due to electrolyte disorders. Chronically present mild to moderate electrolyte disturbances rarely cause seizures. Acute and/or severe depletions commonly do, especially severe hyponatremia (<125 mmol/l in acute, <115 mmol/l in chronic cases), severe hypocalcemia (<1.25 mmol/l; 5 mg/dl), severe hypomagnesemia (<0.4 mmol/l; 1 mg/dl) and severe hypophosphatemia (<0.32 mmol/l; 1 mg/dl). Interictal encephalopathy is common. Infants with gastrointestinal disease and febrile illness and elderly patients under polypharmaceutic treatments are particularly vulnerable groups. Diuretics, desmopressin, SSRI, laxatives in preparation for colonoscopy as well as carbamazepine and derivatives cause hyponatremia. Bisphosphonates may infrequently lead to hypocalcemia, and proton pump inhibitors to hypomagnesemia. Other important causes include malnourishment with a vitamin D deficiency, endocrine disorders such as SIADH and hypoparathyroidism as well as renal disease. Hypernatremia and hypercalcemia may cause seizures occasionally but overall, depletions are more likely than excess states to cause seizures. Hypokalemia and hyperkalemia do not lead to seizures [120,126].

3.2.2.3. Liver and kidney disease as a cause of seizures. Hepatic encephalopathy, notably in acute liver failure, is often accompanied by subtle seizures and non-convulsive status epilepticus [120,127,128]. Uremia can provoke seizures due to uremic neurotoxins, electrolyte disturbances and hypertensive encephalopathy. “Twitch-convulsive-syndrome” with fasciculations, asterixis, myoclonic jerks and seizures typically accompanies uremic encephalopathy. Dialysis dysequilibrium syndrome is now a rare cause of seizures [119,120,129].

3.2.2.4. Inborn errors of metabolism. Even with the increasing availability of genetic studies such as epilepsy gene panels, conventional blood-, urine-, and CSF tests can be of great importance in identifying inborn errors of metabolism, notably in epilepsies of infancy and childhood. In order to identify potentially treatable disorders, various metabolic studies are utilized, some of which are included in newborn blood spot screening tests, while other must be ordered separately. They include glucose (e.g. GLUT-1-deficiency), lactate (e.g. mitochondriopathies), ammonia (urea cycle defects), amino acids (amino acid disorders), copper, coeruloplasmin (Menkes disease), acyl carnitines (organic acidurias, maple syrup disease), pipecolic acid and α-aminoadipic semialdehyde (pyridoxine dependent epilepsy). A full review is beyond the scope of this article, but can be found elsewhere [130].

3.2.3. Intoxication related seizures

Drug- or toxin-induced seizures result from exposure to or withdrawal from prescribed, over-the-counter drugs or illicit drugs and toxins. Suicide attempts with a drug overdose and illicit drug abuse are the most common reasons for intoxication-related seizures in adults and adolescents, while accidental ingestions are more common in younger children [131]. Bupropion, SSRI, tricyclical antidepressants, venlafaxine, antipsychotics, diphenhydramine, tramadol, lithium, theophyllin and anticonvulsant drugs themselves are amongst the most commonly implicated medications, while cocaine, amphetamines, MDMA, phencyclidine and ketamine are the most frequently abused drugs [132–134]. Others include local anesthetics, glycols, betalactam and fluoroquinolone antibiotics, aciclovir, antiparasitics, antifungals, antiarrhythmics, insulin, sulfonylureas, NSAR, immunosuppressives, anticholinergics, antihistamines, cytostatic agents and more. Most drug-related seizures occur within the setting of an overdose or an accumulation in renal impairment. If the medical history is inconclusive and drugs are on the differential diagnosis list, then toxicology screens in urine or blood can be helpful for measuring the drug levels in the blood.

Alcohol withdrawal seizures are the most common toxin-related seizures. Exhaled air or blood alcohol levels are used to measure the current degree of intoxication, elevated carbohydrate deficient transferrin (CDT) and gamma-GT may indicate chronic alcohol abuse. Withdrawal of anticonvulsants, baclofen, sedative-, hypnotic- and gamma hydroxybutyric acid can lead to seizures as well.

Seizures due to chemicals such as heavy metals, hydrocarbons, organophosphates or carbon monoxide, plant- or fungal poisons, e.g. belladonna alkaloids, water hemlock or false morel mushroom are rare in comparison to drug related seizures and require specific testing. A full list of toxins that are implicated in seizures is beyond the scope of this article.

3.2.4. Seizures due to infections

In new-onset seizures, a thorough workup is indicated to rule out infectious, parainfectious or autoimmune encephalitis, meningitis and brain abscess, as these are common and treatable causes of seizures. Fever, headache, meningismus and mental status changes are red flags. Febrile seizures are an important differential diagnosis in children. They affect 2–10% of children aged 6 months to 5 years. Simple febrile seizures are solitary, generalized convulsions that last <15 min, with rapid and full postictal recovery and without the additional neurological signs

and symptoms that most frequently develop in viral illnesses or bacterial infections of the upper respiratory or urinary tract. They are diagnosed on clinical grounds and the same applies for recurrent, simple febrile seizures without additional signs of CNS infection [135]. In <1 year old children and in case of pretreatment with antibiotics, a lumbar puncture is recommended. CSF analysis, imaging studies and empiric treatment are indicated if meningismus is present and in all other scenarios of fever and seizures except typical FC. The laboratory strategies used in the differential diagnosis of neuroinfectious disease must take into account the overall clinical context and include factors such as age, immune status, geographic location, occupation and travel, maternal history in the case of neonatal seizures, etc. They include blood and CSF serological and/or PCR testing for viruses (e.g. herpesviruses, enteroviruses, arboviruses), bacteria (e.g. streptococci, meningococci, staphylococci, listeria, escherichia coli, other gram negative rods, anaerobic gram positive rods and cocci, spirochetes, mycobacteria), fungi (i.e. cryptococcus, candida, aspergillus, histoplasma, blastomyces, coccidioides, sporothrix), protozoa (e.g. toxoplasma, malaria, amebia) and parasites (neurocysticercosis, echinococcus, angiostrongylus, toxocara, trichinella, strongyoides, schistosoma). Seizures can occur in septic encephalopathy. Common febrile illnesses, such as upper respiratory or urinary tract infections, may lower the seizure threshold in patients with epilepsy and be accompanied by typical laboratory changes such as leukocytosis and CRP. A thorough review is beyond the scope of this article, but recent reviews exist [136–146].

3.2.5. Autoimmune mediated seizures

The various types of autoimmune encephalitis display a mostly subacute onset of seizures, psychiatric and memory problems. In the last decade, tremendous progress has been made in characterizing various autoantibodies (e.g. Anti-Hu, Ma2-, GAD65-, NMDA-, AMPA-, $GABA_A$-, $GABA_B$-, mGlu5-Receptor, LGI1, CASPR2, DPPX, TPO) and their variable associations with underlying cancers, unique clinical features and response to immunosuppressive therapy. Demyelating disease, systemic lupus erythematodes, vasculitis and other systemic autoimmune diseases may be another cause of seizures. Due to the rapidly evolving knowledge in this field, we refer to recent reviews elsewhere [147–149].

3.3. Laboratory markers that help detect seizure consequences and complications

3.3.1. Postictal endocrine dysfunction

Numerous studies have examined copeptin levels in critical illness such as stroke, sepsis and myocardial infarction, where elevations indicate a poor prognosis [150]. In ACS, copeptin indicates the presence of myocardial ischemia [151]. As a general stress marker, copeptin displayed mild elevations in perinatal infant stress and in healthy students who were experiencing psychological stress before taking exams [152–174].

In a multicenter, prospective ER study of 389 patients, copeptin levels were found to be elevated after seizures occurred, but they were unable to predict complications such as seizure recurrence, mortality and hospitalizations [175].

Postictal gonadotropin elevations have little relevance in seizure detection or the evaluation of acute complications. They are, however, implicated in reproductive endocrine dysfunctions such as polycystic ovary syndrome, amenorrhea and premature menopause, all of which occur more frequently in women with epilepsy, but can also occur in men with diminished libido and potency. Several reviews are available on the subject [176–178].

3.3.2. Rhabdomyolysis

Rhabdomyolysis, which is the breakdown of muscle fibers, results in the leakage of CK, myoglobin, lactate dehydrogenase, aspartate transaminase and urate. Symptoms include myalgia, muscle weakness and red or brown chromaturia. Less than 5% of GTCS appear to induce rhabdomyolysis with more than a 50-fold increase of CK levels (our own, yet unpublished data). About 7% of rhabdomyolyses are due to GTCS [179,180], particularly alcohol-related and multiple GTCS [63,67,181]. Other causes include drugs, toxins, vigorous exercise, myopathies, endocrine and metabolic disorders, systemic inflammation and trauma. The syndrome is mostly benign, but can lead to acute renal failure (ARF), hyperkalemia, arrhythmia, intravascular coagulation, compartment syndrome, hepatic dysfunction and even death in ~10% of severe cases and up to ~50% of cases that are accompanied by ARF [180].

3.3.2.1. CK: the standard marker for rhabdomyolysis. Mild CK elevations are a physiological response to strenuous physical activity such as in GTCS. Various CK cut-off values define rhabdomyolysis as a 5-fold, 10-fold or 50-fold increase above the upper limits of the reference range. The risk of complications correlates with the CK level. Elevations >15.000 U/l carry a 70% risk of ARF, compared to 35% risk in elevations from 5000–15.000 U/l [182]. Traumatic, septic or ischemic cases lead to more complications than seizure-, exertion- or myopathy related ones. In a clinical study involving 2371 patients, only 6% of seizure-related cases led to the composite outcome of death or renal replacement therapy, as compared to ~40% of cases related to compartment syndrome or sepsis [183]. A risk score that takes into account cause, age, sex, CK and electrolytes, may be used for risk estimates of renal failure and death [183]. Early volume expansion with intravenous isotonic saline is the treatment of choice. Solutions containing potassium and lactate should be avoided.

3.3.2.2. Myoglobin. Myoglobin is the oxygen carrying heme protein of muscle tissues [184]. After muscle fibers are damaged, it is released into the bloodstream within hours, then it is filtered in the glomeruli and reabsorbed in the proximal tubules [184]. If the reabsorption capacity is exceeded, myoglobinuria can cause a reddish chromaturia. Myoglobin can precipitate hypovolemia and increased intratubular pressure, especially under acidemic conditions. Heme can add damage by facilitating renal vasoconstriction and oxidative stress. While CK is a risk marker for rhabdomyolysis-related renal damage, myoglobin is the causative agent. Apart from a short serum half-life of 2–3 h, serum and urine myoglobin measurements display methodological problems. Few studies are available on myoglobin and its relation to seizures. One study reported a rise in serum myoglobin in 8/13 (61%) of GTCS patients; none developed renal damage [185].

3.3.3. Postictal cardiac dysfunction

Many cerebral injuries can cause cardiac dysfunction [186–188]. and ES and SE are among the most prominent [189,190]. This led to the hypothesis that sudden unexpected death in epilepsy (SUDEP) could be caused by cardiac dysfunction in some of the cases.

GTCS lead to an ictal and postictal catecholamine surge, which can mediate microvascular spasms, subendocardial ischemia, tachyarrhythmias and motion abnormalities [191–193]. Indirect signs of catecholaminergic activity (such as ictal tachycardias) are very common and occur in up to 80% of seizures [194]. Simultaneously, intense muscular activity, apnea, tachycardia and increased peripheral and pulmonary vascular resistance expedite increased myocardial oxygen consumption, wall stress and lung fluid flux, which can induce tachyarrhythmias, Takotsubo cardiomyopathy and pulmonary edema.

An alternative mechanism is a seizure-related, autonomic dysfunction with bradycardia and repolarization disturbances, such as QT-prolongation and increased T-wave alternans [195,196]. Attempts have been made to localize specific brain regions to types of arrhythmias such as the temporal lobes and the insular cortex in particular.

3.3.3.1. Postictal elevations of cardiac troponins are not always benign. Cardiac troponins I and T (cTnI, cTnT) are not found in skeletal muscle. CTn is widely used in the diagnosis of acute coronary syndromes (ACS), since it can be detected 3–6 h following the onset of chest pain and peaks after 12–16 h [197].

Cardiac troponin elevations have been reported as unfavorable prognostic markers in cerebrovascular accidents [196,198]. In one study, cTnI elevations were reported in 17 of 89 patients (19%) with acute, critical neurologic conditions. They occurred more frequently in patients who presented with seizures or developed seizures during the course of their disease, although the seizures only affected 7% in this study population [196].

An overview of troponin elevations after seizures is provided in Table 4.

Woodruff and colleagues prospectively measured troponin 8, 24 and 48 h after seizures were monitored in 11 adults without cardiac disease and found no elevations. They concluded that the troponin which is detected after a seizure occurs should never just be attributed to the seizure alone but should instead lead to prompt cardiologic investigations [199].

Alehan and colleagues measured cTnI along with CK-MB and BNP 12 h and 7 days after convulsive seizures in 31 children [200]. They found no elevations of cTnI, but CK-MB and BNP elevations were discovered 12 h after the seizure, which they interpreted as evidence of subtle cardiac dysfunction. Of note, the postictal ECGs were normal for all of the children.

In an ER study involving 49 patients aged 12–65 years with ES and without cardiovascular risk factors, no elevations of cTnI or other cardiac anomalies were found. Patients with repetitive seizures did have higher cTnI levels, but their levels still remained within the normal range [201].

Another study [202] investigated a group of 60 adult patients who were referred to the ER after GTCS. ECG and echocardiography tests were performed to exclude those patients with preexisting cardiac conditions. The patients were then divided into two subgroups defined by the presence of hypoxia ($sO_2 < 90\%$). The cTnI remained within the normal range for both groups, but the mean cTnI value was significantly higher for the hypoxic group. The authors attributed this to subtle cardiac injury.

A retrospective ER study detected cTNI elevations in 18 of 279 (6.5%) patients. ECG and echocardiography testing revealed

Table 4
Summary of studies examining troponin elevations in epileptic seizures and status epilepticus. Elevations of cardiac troponin can be found in 6.7% of all reported 1469 seizure patients and in 21.3% of 357 SE patients. The data are insufficient for providing estimates for individual seizure types. Most cases of troponin elevations that occur after a single seizure appear benign, but serious events such as myocardial ischemia or Takotsubo syndrome may occur in 7.1% of seizure-related troponin elevations (~0.5% of seizures). In SE, the rate of serious cardiac events appears to be higher, but exact data are not yet available.

	Author	Groups	Age	Setting	Time	Elevated Troponin	Other Outcomes
epileptic seizures	Woodruff, 2003 [199]	7 CPS. 4 GTCS patients	19–55	Video EEG monitoring, prospective	Baseline, 8, 24 and 48 h	No cTNI or cTNT elevations	ECG normal in all patients.
	Alehan, 2009 [200]	12 FC 19 GTCS 50 healthy patients	0.9–16	ER, prospective	12 h after event and daily for 7 days	No cTNI elevations	ECG normal in all patients. BNP and CKMB elevated in FC and GTCS.
	Hajsadeghi, 2009 [201]	49 GTCS patients	12–65	ER, prospective	6 h after event and daily for 10 days	No pathological elevations but higher cTNI after multiple seizures	No cardiac pathology in ECG or TTE.
	Eskandarian, 2011 [202]	60 GTCS Patients, 50% with hypoxia.	>12	ER, prospective	6th and 10th days after seizure	No pathological cTNI elevations but higher cTNI in patients with transient postictal hypoxia	No cardiac pathology in ECG or TTE.
	Schneider, 2010 [203]	279 ES patients	Not provided	ER, prospective	Not provided	18/279 (6.5%) cTNI elevations	Takotsubo syndrome in 5/18 patients.
	Sieweke, 2012 [70]	741 GTCS patients	17–89	ER, retrospective	On admission	50/741 (6.7%) cTNI elevations	No cardiac pathology in ECG. TTE or PTCA. Associated with age, elevated CK, vascular risk factors.
	Fawaz, 2014 [204]	14 GTCS patients	19–84	ER, retrospective	On admission	4/14 (28.6%) cTNT elevations	No cardiac pathology in ECG. Associated with age and vascular risk factors.
	Our own, yet unpublished data	75 GTCS	13–88	ER, retrospective	Within 24 h after admission	9/75 cTNI elevations (12%)	One case of NSTEMI and of STEMI.
status epilepticus	Chatzikonstaninou, 2015 [205]	20 SPS 50 CPS 177 GTCS 38 SE	Adult	ER, retrospective	On admission	Overall: 27/247 (9,7%) SE: 10/38 (26.3%) ES: 17/209 (8.1%) cTNI elevations	No cardiac pathology in ECG. Associated with age, SE, temporal lobe epilepsy, vascular risk factors.
	Soundarya, 2014 [208]	266 SE (NCSE, GTCE) excluding postanoxic.	>18	ICU, retrospective	During SE or within 24 h after diagnosis	57/266 (21.4%) cTNI elevations	Associated with vascular risk factors but not with age. Higher 30 day mortality in cTNI patients.
	Hocker, 2013 [209]	23 RSE	Adult	ICU, retrospective	After onset of SE	9/23 (39.1%) cTNI elevations	Pathologic findings in multiple patients, e.g. arryhtmias, ST-changes, systolic dysfunction. One case of NSTEMI.
	Mehrpour, 2013 [210]	30 GTCSE, cardiac disease excluded	12–60	ICU, retrospective	Within 24 h after admission.	No cTNI elevations	No cardiac pathology reported.

Takotsubo cardiomyopathy in five patients, none of whom complained of cardiac symptoms. In the other 13, no pathologic findings (e.g. ACS) were diagnosed. The specific numbers were not published for these subgroups, nor were the seizure types that were encountered [203].

A large, retrospective ER study investigated cTnI in 741 patients with GTCS. From this group, 50 (6.7%) showed a cTnI release. All patients underwent echocardiography and ECG studies and a coronary angiography was performed on 19. Neither ACS nor Takotsubo syndrome were observed. CTnI elevations were associated with higher age, elevated CK, further CK increases and vascular risk factors. The authors concluded that cTnI elevations are mostly found in patients with vascular risk factors and prolonged seizures which they indirectly inferred from the higher rates in CK [70].

A smaller ER study reported cTnT elevations in 4 out of 14 patients (28.6%) [204]. The affected were elderly and had cardiovascular risk factors. ECG exams did not demonstrate myocardial ischemia. The percentage of cTnT elevations seems rather high, but may reflect the rather low patient number. Interestingly, patients with CK elevations were excluded, which demonstrates that cTnT elevations can occur independent of CK.

Another ER study [205] measured cTnI in 247 patients with ES or SE and found elevations in 8.9% of ES and 26.3% of SE cases (n = 38). Preexisting CAD, vascular risk factors and a temporal seizure focus increased the risk. ECG examinations revealed no myocardial ischemia.

While single seizures are a benign event in most cases, SE carries a significant morbidity and mortality risk. Cardiac changes during SE play a major role, as demonstrated by ECG and post mortem studies [206,207]. A retrospective analysis on cTnI values in 266 patients with SE found elevations in 31% of patients with additional vascular risk factors (n = 166) and in 8.7% (n = 66) without additional vascular risk factors (n = 66) [208].

A retrospective investigation on cardiac injury in refractory SE found troponin elevations in 9 of 23 patients (39.1%) [209]. Overall, signs of cardiac injury were found in two-thirds of patients both with and without preexisting risk factors. A trend towards higher mortality in the group with cardiac injury did not reach statistical significance. The authors discuss both the role of neurocardiogenic stress as well as highly dosed anticonvulsants and anesthetic agents in the high rate of cardiac abnormalities encountered.

Another study on generalized SE included 30 patients aged 12–60 without preexisting cardiovascular diseases and revealed contrasting results. No elevation of cTnI was found. The authors explained this important discrepancy by stating that their patients were less severely affected and preexisting cardiovascular problems were excluded. They concluded that cTnI is too insensitive to accurately measure subtle changes in cardiac disturbances found in SE [210].

These data suggest that troponin measurements after a single GTCS are not generally warranted, but may be particularly useful in patients who are older than 50 years of age, have preexisting cardiovascular risk factors or heart disease, and who suffer from a status epilepticus. If troponin elevations are found after a seizure, a cardiac workup is recommended.

3.3.3.2. Postictal changes of natriuretic peptides may indicate subtle cardiac dysfunction. Natriuretic peptides (ANP, BNP, CNP) possess natriuretic, diuretic and vasodilatory effects. BNP and its precursor, NT-pro-BNP, help assess heart failure and may have implications for stroke care [211–215].

The release of natriuretic peptides while seizures occur was first detected in a rodent model [216] and later demonstrated in a case report involving seizures, polyuria and pyrexia [217].

An ER study [218] assessed BNP and NT-pro-BNP in 65 children with FC (n = 33), GTCS (n = 12), partial ES (n = 16), syncope (n = 4) and controls (n = 31). A significant, 1.5- to 2-fold increase in NT-pro-BNP 4 h postictally was revealed in children with GTCS and FC, particularly in prolonged FC. NT-pro-BNP returned to baseline after 24–48 h. Cardiologic examinations were normal.

A similar study [200] in 31 children with FC or GTCS demonstrated that BNP increased ~3-fold 12 h after seizures occurred and returned to normal within 7 days. The CK-MB was increased ~1.5-fold, while troponin and ECGs remained normal, thus indicating subtle cardiac dysfunction.

3.3.4. Postictal, acute renal failure

Rhabdomyolysis, postictal lactic acidosis, hyperthermia and hypovolemia are mediators of ARF which occurs after a GTCS [185,219–222]. While frank ARF is rare, there is convincing evidence for subtle renal damage at least in GTCS and FC [185,223]. Treatment includes fluid substitution, urine alkalization and dialysis, if needed.

3.3.5. Postictal elevations of uric acid can contribute to acute kidney injury

Uric acid is the final product of human purine metabolism. During seizures, nucleosides are released from muscles, neurons and glia. Serum nucleotidase activity is increased for ~60 min postictally, which may further the production of uric acid [224].

Two case series involving GTCS or SE reported increases in serum uric acid and ARF [220,225]. Increased muscle protein breakdown and excess release of hypoxanthin from hypoxic tissues were suggested mechanisms [226]. One case report described generalized SE without rhabdomyolysis, but with hyperuricemia, lactic acidosis, hyperthermia and hypovolemia. These conditions increase the likelihood of urate precipitation. In this case, the constellation led to urate nephropathy-mediated ARF [221].

3.3.6. Transient lactic acidosis: a typical consequence of GTCS

The degree of lactic acidosis is not correlated with the neuropathologic damage in SE [88]. A single study found severe lactic acidosis to be a risk factor for recurrent seizures in the following 4–6 h, particularly with a pH < 7.245 or a lactate >7.65 mmol/L [227]. For more information on lactate, see Section 3.1.3.2.

3.3.7. Postictal liver dysfunction must prompt a review of the administered anticonvulsants

Mild to moderate elevations of liver transaminases are commonly found in patients taking anticonvulsants, whereas signs of abnormal liver function are uncommon following a single, uncomplicated seizure. In contrast, hepatic dysfunction and frank liver failure can follow prolonged seizures and status epilepticus, mostly within the context of polypharmacotherapy and especially in those patients with POLG mutations [228–230]. AEDs such as valproate, phenytoin, carbamazepine, phenobarbital, felbamate (and less often lamotrigine) may lead to elevated liver enzymes and even liver failure [231].

3.3.8. GTCS are followed by subtle changes in glucose and electrolytes

Glucose may increase slightly during seizures and can be expected to fall within the normal or slightly elevated range postictally [89,121]. Postictal glucose mostly depends on the preictal glucose level. GTCS may lead to transient hypernatremia due to shifts of extra- and intracellular osmolytes [126]. Postictal hyperkalemia may indicate rhabdomyolysis or renal injury after GTCS.

3.3.9. Postictal inflammatory reactions are mostly benign but can indicate an infectious complication

Apart from inflammation as a cause of seizures, ES and especially SE inversely lead to an inflammatory reaction with transient hyperthermia, leukocytosis and elevation of inflammatory cytokines.

Postictal changes in the blood count include leukocytosis, which is attributed to vigorous muscular activity and the periictal release of catecholamines, cortisol and proinflammatory cytokines.

Postictal leukocytosis tends to be moderate with an average increase of ~5000/μl after GTCS and ~2500 after CPS, and resolves within 24 h [193,232]. One video-EEG monitoring study of 22 patients reported a mean postictal leukocyte increase of 13% after CPS and an increase of 138% after GTCS [193], Leukocytosis is correlated with epinephrine release. Another video-EEG study demonstrated leukocytosis after 36% of GTCS and 7% of CPS, but not after SPS or PNES [20]. Two ER studies found leukocytosis in 37.1% and 48.4% of patients with seizures as secondary study parameters [77,80]. A study on SE showed leukocytosis from 12,700 to 28,000/μl in 62% of cases that was unrelated to infection [88].

After seizures occur, the interpretation of leukocytosis must be conducted within the context of the overall clinical picture. In the case of new-onset seizures, hyperthermia and leukocytosis, infections must be ruled out. Depending on the overall clinical picture, treatment may be limited to a careful physical exam and a repeated laboratory test or lead to more expansive testing involving lumbar punctures, imaging and empiric administration of antibiotics.

Apart from leukocytosis, seizures lead to a transient, but marked, inflammatory response with release of cytokines such as interleukin-1beta, interleukin-6 and tumor necrosis factor alpha. A detailed review is available by Li and colleagues [233]. Marked or sustained elevations of c-reactive protein, procalcitonin and other clinical markers of a systemic inflammatory response should not be attributed to a seizure alone, and should prompt the search for an infectious etiology or complication. Aspiration pneumonia is one particular infection which should be taken into consideration. It develops in ~0.3% in otherwise healthy GTCS patients, but is far more common in the multimorbid elderly and particularly in those patients who are institutionalized or intellectually disabled [234].

3.3.10. The prognostic value of protein S100-B after single GTCS is very limited

In a multicenter, prospective study of 389 patients, serum S–100B was found to be elevated after seizures occurred, but it could not predict seizure recurrence, mortality or rehospitalization [175]. For more information on S100, see Section 3.1.4.2.

3.3.11. Other postictal complications

While laboratory tests can help in the management of seizure-related injuries and psychiatric complications, they are, first and foremost, detected and monitored clinically and are therefore not part of this review.

4. Conclusions

In conclusion, we will attempt to answer the short, but clinically relevant, question, "What laboratory tests are useful after seizures occur?"

4.1. Diagnosis of an event type: ES, PNES or syncope?

No laboratory values can definitely prove or rule out epileptic seizures. CK and PRL elevations can provide valuable information in support of an ES diagnosis, provided that the blood samples are drawn at the appropriate time points (PRL within 20 min postictally, CK at any time postictally with an expected peak after 24–48 h). Transient leukocytosis, hyperammonemia and lactic acidosis may also point towards GTCS if samples are drawn quickly after the event. The exact kinetics for these markers are still unknown.

4.2. Diagnosis of etiology: what is causing the seizures in my patient?

For those seizures with an unknown cause, simple blood tests can be of value in order to quickly determine the etiology in the case of glycemic or electrolyte derailments, renal or liver failure, thyrotoxicosis and myxedema. If inborn errors of metabolism are suspected, screening panels or hypothesis driven, specific tests can be applied. Marked or prolonged leukocytosis, elevated C-reactive protein or procalcitonin point towards neuroinfectious disease or septic encephalopathy and should be followed-up. Lumbar punctures with virology and microbiology testing are recommended in this case (excluding typical, febrile convulsions). Autoantibody panels are now commonly used and permit early detection of limbic encephalitis. Both toxicology screening and the measurement of serum drug levels in prescription drugs help identify intoxication or withdrawal-related seizures.

4.3. Prognostication: what complications can arise from a given seizure?

CK, electrolytes, creatinine, liver and renal function tests should be conducted at least once for a GTCS that was considered sufficiently severe by the patient (or their caregiver) to present at an ER, especially after prolonged seizures, status epilepticus and after the first seizure. Significant elevations in CK which are detected early on may indicate rhabdomyolysis and renal failure in the days to follow and should lead to hospital admission. In cases involving postictal, acute renal failure without rhabdomyolysis, the elevated uric acid could be the culprit. Troponin elevations occasionally point towards myocardial infarction, stress cardiomyopathy or other grave cardiac complications, but are benign in most cases. A 12-lead ECG and repeated measurement of troponin should be performed in all patients with troponin elevations, and a more comprehensive cardiac workup is advisable at least for those patients with cardiovascular risk factors or for patients older than 50 years of age (if patients display no other clinical signs of myocardial infarction).

Conflicts of interest

R. Surges has received speaker fees or honorary for serving on the advisory board from Bial, Cyberonics, Desitin, EISAI, Novartis and UCB Pharma. C.E. Elger has received speaker fees from EISAI, Novartis and UCB Pharma. The authors declare that there is no conflict of interest regarding the publication of this paper.

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