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ORIGINAL ARTICLE

Study of the Acute Metabolic Effects in Children with Tonic-Clonic Seizures

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ABSTRACT

Background: Tonic-clonic seizures (TCS) have a lot of metabolic processes inside the body, leading to metabolic responses in all systems, including the brain, muscles, liver, kidneys, and blood. This study aimed to differentiate if tonic-clonic seizures were of epileptogenic or non-epileptogenic originand examine alternative biomarkers for accurate differentiation.

Methods: Our case-control study was performed in the Pediatrics department at Zagazig University Hospital. A total of 120 individuals were divided into two groups. The first group consisted of children aged six months to fifteen years experiencing tonic-clonic seizures, while the second group included matched healthy children as controls. Blood markers, including lactate, ammonia, and creatine kinase (CK), were analyzed to assess their effectiveness in differentiating between the two groups.

Results: The study revealed a significant elevation in lactate levels among cases compared to the control children ($P < 0.001$).Ammonia levels were also significantly higher among the patients than controls ($P < 0.001$). Furthermore, the study found a positive correlation between the duration of tonic-clonic seizures and lactate levels in the blood ($P=0.016$), highlighting lactate's potential utility as an indicator of seizure severity.

Conclusions: The study underscores the significance of monitoring lactate and ammonia levels during TCS episodes as valuable indicators of seizure severity and metabolic disturbances.

Keywords: Acute Metabolic Effects, children, Tonic-Clonic Seizures

INTRODUCTION

One of the most frequent neurological illnesses is epilepsy. A Recent meta-analysis found that the incidence rate of active epilepsy was 61.44 per 100,000 people, while the point prevalence is 6.38 per 1,000 people. The yearly sudden unexpected death in epilepsy (SUDEP) incidence rate is around 1 in 1000 instances of epilepsy per year, but in severe situations, it can reach 9 in 1000 cases [1].

A tonic-clonic seizure (TCS) manifests itself in stiff involuntary muscle contractions. Cyanosis and a first cry may accompany seizures in which the respiratory muscles stiffen. Sometimes, the tongue gets bitten. Urinary incontinence may develop. If the patient slips and falls, they could hurt

themselves. Extreme salivation and frothing are possible during the clonic phase [2].

Seizures result in unique metabolic alterations. Catecholamines and prolactin are two examples of hormones produced by the neuroendocrine system, which are triggered to production by high levels of neuronal stimulation. Catecholamine production and whole-body muscle contractions increase oxygen demand in the brain, muscles, and heart, while poor breathing slows down compensatory mechanisms. Lactate, ammonia, and urea are released by strained tissues, whereas creatine kinase and myoglobin are released by irritated skeletal muscles [3].

Differential diagnosis and understanding of TCS's pathophysiology and potential consequences, such as sudden unexpected death in epilepsy (SUDEP), may be aided by changes in related blood markers [4]. Skeletal muscle and neurons, two metabolically active cells, contain relatively high creatine levels because of their central role in cellular energy metabolism. However, creatine kinase (CK) discriminative power in non-epileptic seizures was claimed to be limited [5].

Anaerobic metabolism during muscle contractions results in the production of lactate. The lactate levels in the blood after an attack have been recommended as a paraclinical aid for differentiating epileptic from non-epileptic seizures [6].

So, we aimed in thisstudy to differentiate if tonic-clonic seizures were of epileptogenic or non-epileptogenic origin and examine alternative biomarkers for accurate differentiation.

SUBJECTS AND METHODS

From June 2022 to July 2023, this case-control study was done at Zagazig University Pediatric Hospital. The study's sample size was calculated using Open Epi at 80% power and 95% CI. It included 120 cases (60 children aged six months to 15 years old diagnosed with tonic-clonic seizures or a history of previous CTS and 60 control).

Inclusion Criteria: Cases aged between 6 months and 15 years old suffering from tonic-clonic seizures from both sexes and the control group, healthy children from both sexes aged between 6 months and 15 years were included.

Exclusion criteria:Children younger than five months or older than 15 years and patients who had liver, renal, heart, or any CNS comorbidity of autoimmune, infectious, or oncologic etiology.

This study followed the guidelines [the World Medical Association's Code of Ethics (Declaration of Helsinki) for human studies]. All parents of participants provided informed and written consent. The Institutional Review Board has approved this research (#9361/26-03-2022).

All the included children were subjected to entire history taking including personal, complaint, present, past, perinatal, and developmental dietetic history. Clinical examination was done, including general and neurological tests.Electrocenaphlography (EEG) and Magnetic resonance imaging (MRI) were performed on all participants. The usual diagnostic procedure included a 3 Tesla MRI of the brain, neuropsychological testing, and continuous video-EEG monitoring with either noninvasive scalp EEG (10-20 systems with additional temporal electrodes) or, in rare cases, invasive EEG. Blinded to the results of the blood samples, the clinical aspects of TCS were evaluated, including the existence and duration of postictal generalized EEG suppression (PGES),the semiology of TCS, and the

duration of the tonic-clonic phase of TCS.

Laboratory investigations included complete blood count (CBC), kidney function tests,liver enzymes, Erythocyte sedimentation rate (ESR), and C reactive protein (CRP), with assessment of creatine kinase, lactate, and ammonia.

Baseline (when informed consent was given before TCS occurred) and post-TCS (at varying periods) blood samples were taken (within 30 minutes after TCS as well as after 2, 6, 24, and 48 hours after a TCS). Two serum samples, two EDTA, one sodium citrate, and one sodium fluoride sample were used. Complete blood count was performed on Sysmex Xn 330 cell counter (Sysmex corporation, Japan). Liver enzymes, kidney functions, and CK, Lactate and ammonia were measured by spectrophotometry on Roche Cobas 8000 (c702 module) using dedicated reagents from manufacturer (Roche Diagnostics, Germany). CRP was measured turbidimetrically on Roche Cobas 6000 (c501 module) using dedicated reagents supplied by manufacturer (Roche Diagnostics, Germany). ESR was measured using Vision ESR analyzer (YHLO Biotech Co., China).

Statistical Analysis

Information gathered from a patient's medical history, physical examination, and laboratory tests were coded, processed, and analyzed in Microsoft Excel. The Shapiro-Wilk test was utilized to check for a normal data distribution. The gathered data were loaded into SPSS 20.0 (Statistical Package for the Social Sciences) to conduct statistical analysis. The indicated differences between qualitative variables were computed using the Chi-square and Fisher exact tests. For non-parametric quantitative variables, the Mann-Whitney test and Independent T were employed to determine the significance of the gap between the two groups. Normal variables were correlated using Pearson's correlation, and non-parametric variables were correlated using Spearman's correlation.

RESULTS

Age and sex were comparable in both but without statistically significant differences (Table 1).

The most common type of seizure among the cases group was asymmetric or bilateral tonic arm flexion (80%). In comparison, the most prevalent findings in EEG were diffuse slowing (48.3%) and PGES (45%). The most prevalent zone among patients was temporal (53.3%), followed by generalized (16.7%) and frontal (11.7%) (Table 2).

Total leucocyte count (TLC), creatinine, urea, CRP, and ESR were significantly higher among cases compared to the control group($p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$ respectively) (Table 3).

Lactate and ammonia were significantly higher among cases compared to the control group ($p<0001$ per each). However, creatine kinase was more elevated among patients compared to the control group but without a statistically significant difference (Table 4).

There was a significant positive correlation between the duration of seizures and lactate among the cases group ($p=0.011$) (Table 5).There was a significant positive correlation between the duration of the tonic-clonic phase and lactate among the cases group ($p=0.016$)((Table 6 and Figure 1).

Table (1): Demographic data of the two studied groups

Variable		**Cases** (n=60)	**Control** (n=60)	**t / χ^2**	**P**
Age (years) Mean ± SD Range		6.98 ± 3.41 1 – 15	6.75 ± 3.01 2 – 15	.398	.962
Sex	Female	26 (43.3%)	33 (55%)	1.63	.201
	Male	34 (56.7%)	27 (45%)		

Table (2): Types of tonic clonic seizures EEG findings and Epileptogenic zone distribution among the cases group.

	Cases (n=60)	
	N	**%**
Types		
Asymmetric or bilateral tonic arm flexion	48	80%
Bilateral symmetric tonic arm extension	8	13.3%
Clonic without tonic extension	4	6.7%
EEG		
Alpha	4	6.7%
Diffuse slowing	29	48.3%
PGES	27	45%
Epileptogenic zone distribution		

	Cases (n=60)	
	N	**%**
Epileptogenic zone		
Temporal	32	53.3%
Generalized	10	16.7%
Frontal	7	11.7%
Multifocal	5	8.3%
Hemispheric	4	6.7%
Parietal	2	3.3%

PGES: Post ictal generalized EEG suppression

Table (3): Routine laboratory parameters between the two studied groups.

	Cases (n=60)	**Control** (n=60)	**t**	**p**
Hemoglobin (g/dl) Mean ± SD	12.47 ± 1.14	12.62 ± 1.13	.741	.460
TLC ($x10^3$/L) Mean ± SD	12.1 ± 4.7	6.1 ± 1.27	**MW 91.5**	**0.001**
PLT ($x10^3$/L) Mean ± SD	308.37 ± 46.72	296.67 ± 55.61	1.25	0.215
ALT (U/L) Mean ± SD	30.25 ± 5.28	28.63 ± 4.62	1.78	0.077
AST (U/L) Mean ± SD	30.45 ± 4.87	29.23 ± 4.5	1.42	0.158
Creatinine (mg/dl) Mean ± SD	1.13 ± 0.227	0.73 ± 0.135	**12**	**<0.001**
Urea (mg/dl) Mean ± SD	28.17 ± 5.34	19.6 ± 5.41	**8.73**	**<0.001**
CRP (mg/l) Mean ± SD	20.38 ± 7.83	1.54 ± 0.96	**MW 9.45**	**<0.001**
ESR (mm/hr) Mean ± SD	34.15 ± 4.85	20.23 ± 6.24	**13**	**<0.001**

PLT: platelet, ALT:Alanine transaminase AST:Aspartate aminotransferase , CRP: C reactive protein, ESR: Erythrocyte sedimentation rate

Table (1): Laboratory parameters between the two studied groups.

	Cases (n=60)	**Control** (n=60)	**MW**	**p**
Creatine kinase (U/L) Mean ± SD	95.63 ± 47.38	86.32 ± 27.18	1683	.539
Lactate (mmol/L) Mean ± SD	12.78 ± 5.54	0.79 ± 0.412	**10.5**	**<0.001**
Ammonia (µmol/L) Mean ± SD	136.47 ± 82.57	22.28 ± 6.05	**31**	**<0.001**

Table (5): Correlation between duration of seizures and other parameters among cases group.

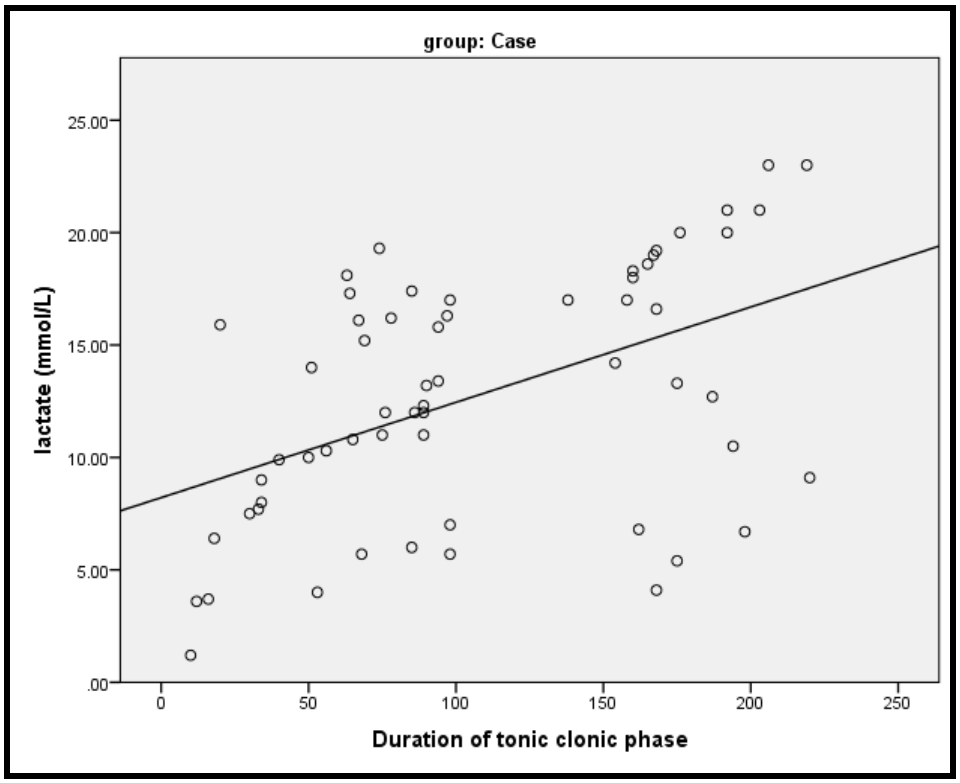
	Duration of seizures	
	R	**p**
Hb	-0.087	0.508
TLC	0.013	0.923
PLT	0.041	0.754
ALT	0.027	0.840
AST	0.146	0.267
Creatinine	0.020	0.882
Urea	0.198	0.130
CRP	0.045	0.734
ESR	0.105	0.191
Creatine kinase	0.223	0.087
Lactate	**0.327**	**0.011**
Ammonia	0.170	0.194

Hb: Hemoglobin, TLC: total leucocyte count, PLT: platelet, ALT: Alanine transaminase AST: Aspartate aminotransferase , CRP: C reactive protein, ESR: Erythrocyte sedimentation rate

Table (6): Correlation between duration of tonic clonic phase and other parameters among cases group.

Parameter	**Duration of tonic clonic phase**	
	r	**P**
Hb	-0.029	0.828
TLC	.0175	0.181
PLT	-0.113	0.392
ALT	0.252	0.052
AST	0.189	0.148
Creatinine	0.196	0.134
Urea	0.237	0.068
CRP	0.113	0.389
ESR	0.062	0.638
Creatine kinase	0.096	0.463
Lactate	**0.310**	**0.016**
Ammonia	0.168	0.369

Hb: Hemoglobin, TLC: total leucocyte count, PLT: platelet, ALT: Alanine transaminase AST: Aspartate aminotransferase , CRP: C reactive protein, ESR: Erythrocyte sedimentation rate



Figure(1): Correlation between duration of tonic clonic phase and other parameters among cases group.

DISCUSSION

Tonic-clonic seizures represent a prevalent seizure type that profoundly influences the body's metabolic processes. These seizures trigger intricate metabolic responses spanning various bodily systems, including the brain, muscles, liver, kidneys, and blood [4].

A pivotal metabolic alteration occurring during a TCS is the escalation of lactate production. Lactate is a byproduct of anaerobic metabolism, a method of generating energy without the presence of oxygen. During a TCS, the brain's demand for oxygen surges dramatically, yet the oxygen supply cannot keep pace. Consequently, anaerobic metabolism intensifies, leading to an upswing in lactate production. The heightened lactate production initiates a cascade of additional metabolic shifts, encompassing acidosis, hyperammonemia, and hypophosphatemia [7].

Therefore, the present study aimed to evaluate the differential diagnosis of tonic-clonic seizures, whether epileptic or non-epileptic. The study involved 120 individuals divided into two groups. The first group included children from both sexes between six months and fifteen years old suffering from tonic-clonic seizures. The second group included matched healthy children as a control. Previous research has often used markers found in the bloodstream to differentiate between different types of transient loss of consciousness (TLOC).) Creatine kinase (CK) and Prolactin (PRL) have been utilized as the most commonly employed blood markers for differential diagnosis of TCS, exhibiting a high specificity (>90%) with a lower sensitivity [3,8].

New evidence suggested that additional biomarkers may better distinguish TCS from other causes of TLOC. It has been shown, for instance, that ammonia can differentiate TCS from different kinds of TLOC in several emergency room (ER) studies and one prospective video EEG monitoring study.

Despite the prevalence of postictal lactic acidosis, relatively few research have looked into lactate as a diagnostic measure following TCS [4]. However, when TLOC is the primary concern, lactate is proposed as a somewhat sensitive and specific marker of TCS [9].

The present study examined the differences between Lactate, Ammonia, and Creatine kinase among the two study groups. The mean lactate level in the case group was significantly higher compared to the control group, P< 0.001. This finding indicates a substantial lactate elevation in individuals who experienced tonic-clonic seizures. Elevated lactate levels have been associated with various metabolic disturbances, including hypoxia, mitochondrial dysfunction, and impaired glucose metabolism. It is well-documented that seizures, especially tonic-clonic seizures, can lead to increased energy demands and oxygen consumption in the brain. Consequently, lactate accumulation could reflect anaerobic metabolism during seizures as the brain switches to alternative energy sources due to increased demand. Consistent with this finding, several studies reported that TCS increases lactate levels in children. For example, a recent multi‐center observational study found that lactate concentration in blood increases immediately after a tonic-clonic seizure, presumably due to muscle hypoxia during convulsions [10].

In another study, researchers showed that elevated lactate levels persist for at least 30 minutes after a seizure ends, making it a reliable metabolic marker of Tonic-clonic seizures. In addition, over 90% of seizures had raised serum lactate levels that returned to baseline within 2 hours, suggesting that shorter periods are required to employ lactate as a valid biomarker of Tonic-clonic seizures [4].

Furthermore, a recent systematic review and meta-analysis found that patients with generalized tonic-clonic seizures had higher serum lactate levels than patients with other seizure types [11].

In addition, tonic-clonic epileptic occurrences can be distinguished from febrile seizures, syncope, and psychogenic nonepileptic seizures in children by measuring serum lactate within two hours after occurrence [12]. Besides, Serum lactate was identified as a sensitive and specific diagnostic marker for distinguishing generalized tonic-clonic seizures (GTCS) from syncope, particularly in the first and second hour after the event [13].

The current study also positively correlated blood lactate levels with Tonic-Clonic Seizure duration (P= 0.011). There was a significant relationship (P= 0.016) between blood lactate levels and the length of the tonic-clonic phase. Despite this, another study indicated that patients whose serum lactate levels were within the normal range stayed much longer in the emergency room than those whose lactate levels were above the normal range. Consequently, the authors concluded that higher serum lactate levels due to a seizure do not directly correlate with biomarkers of disease severity or prognosis [14].

Overall, the elevated lactate levels observed in this study and these previous studies may have clinical implications. It suggested that monitoring lactate levels during and after seizures could be a valuable marker for assessing tonic-clonic seizures' severity and metabolic impact [4].

Second, the current study demonstrated a significant difference in ammonia levels between the cases and control groups. The mean ammonia level in the cases group was

markedly higher compared to the control group, p-value < 0.001. Ammonia is primarily a byproduct of amino acid metabolism and is detoxified by the liver. Elevated ammonia levels in the blood indicate impaired liver function or increased ammonia production. In the context of seizures, this finding could be attributed to increased muscle activity, as intense muscle contractions characterize seizures. The breakdown of muscle tissue during seizures may release ammonia into the bloodstream, contributing to the observed elevation [15].

Previous studies reported that ammonia levels might be elevated in children with tonic-clonic seizures. The prevalence of hyperammonemia in seizure patients was 67.77%, with generalized tonic-clonic seizure patients having the highest plasma ammonia levels [16].

One further study revealed that elevated ammonia levels are a strong indicator of a recent history of either a generalized convulsion or a generalized tonic-clonic seizure, which may aid in the diagnostic process [17].

It was proposed that ammonia levels be included in a classification model for epileptic seizures because they correlate most strongly with the diagnosis of epileptic seizures from the prediction model [18].

Seventy percent of patients with tonic-clonic seizures had elevated ammonia levels 30 minutes after the seizures stopped, and 71 percent had ammonia levels more than twice the upper limits of normal [3].

Additionally, Sharma et al. [18] found that Serum valproic acid levels were associated with blood ammonia levels, and high-dose valproic acid monotherapy resulted in significantly higher blood ammonia levels compared to low-dose treatment in epileptic children.

On the other hand, the present study did not find a statistically significant difference in the creatine kinase (CK) level between the two study groups. The relationship between tonic-clonic seizures and creatine kinase (CK) levels has been investigated in several studies. For example, Matz et al. [13] compared serum lactate and CK concentrations in individuals following generalized tonic-clonic seizures and syncopes. Their findings suggested that early postictal serum lactate concentrations were more effective than CK concentrations in distinguishing between these conditions. Similarly, Nass et al. [3]examined the value of blood tests performed after an epileptic seizure to determine the cause and severity of the attack. While their study encompassed a broader range of blood markers, it provided insights into the limited utility of CK levels as a sole diagnostic marker for seizures.

Furthermore, Brigo et al. [8] conducted a systematic review explicitly focusing on postictal serum CK levels for differentiating epileptic seizures from psychogenic non-epileptic seizures. Their study highlighted the potential limitations of CK as a stand-alone marker for distinguishing between these seizure types.

These studies aligned with the current study, suggesting that while CK levels may provide some information regarding muscle damage in the context of tonic-clonic seizures, they are insufficient for reliable differentiation or diagnosis. Instead, other biomarkers, such as serum lactate, may hold more significant promise in this regard [11].

The present study also compared different routine laboratory parameters between the two groups, including Hemoglobin, total leucocyte count (TLC), platelet count (PLT),

Erythrocyte sedimentation rate (ESR), CRP, liver enzyme, and kidney function. The results revealed that specific parameters, like hemoglobin, platelet counts, and liver enzymes, were not statistically significant between the two groups. On the other hand, there are notable statistical variations in parameters such as TLC, creatinine, urea, CRP, and ESR between the two groups. These variations highlight the significance of considering the broader systemic effects of seizures. It underscores the need for a thorough clinical evaluation and management approach for individuals with epilepsy. The changes in routine blood parameters in TCS patients were investigated earlier; however, limited studies exist. A recent retrospective study examined the variations in typical blood markers in those with generalized tonic-clonic seizures (GTCS). When comparing GTCS patients to controls, the authors found that their platelet count, red blood cell count, white blood cell count, neutrophil count, lymphocyte count, and neutrophil-to-lymphocyte ratio (NLR) were all higher at the commencement of the GTCS episode. Precisely, The neutrophil count and WBC count in GTCS cases with a seizure duration of less than 5 minutes were significantly lower than those with more than 5 minutesHuang et al. [20].

Another Turkish study by Güneş and Büyükgöl [21] examined the connection between widespread inflammation and epileptic attacks. Important inflammatory biomarkers include the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR).

On the other hand, Nardone et al. [22]linked electrolyte disturbances, which seizures and kidney function might cause influences. The authors linked seizures, typically of the generalized tonic-clonic variety, to severe and fast-progressing hyponatremia. When the sodium concentration in the blood drops below 120 mmol/L, this condition is often the result.

This study also found a highly significant level of CRP and ESR in the case group than in the control. These findings highlighted the connection between Tonic-clonic seizures and inflammatory markers. Seizures can trigger systemic changes in the body, including increased body temperature, elevated white blood cell count, and elevated C-reactive protein levels, resembling an inflammatory response [23].

In addition, CRP levels were significantly higher in patients with generalized epileptic seizures compared to healthy controls [21], which was aligned with the current results.

Moreover, Faria et al. [24] found that some patients had increased myocardial necrosis/dysfunction biomarkers after seizures, including high-sensitivity C-reactive protein (hs-CRP).

Limitations

There are certain limitations in our study. Firstly, the sample size might be relatively small, with 60 subjects in each group. The results may not apply to a broader population because of this; understanding if tonic-clonic seizures are of epileptogenic or non-epileptogenic origin may require a more significant and more representative sample. Secondly, since the study was conducted in a single outpatient clinic of a specific hospital, there is a potential for selection bias. The patient population might not fully represent the diversity and characteristics of all individuals with tonic-clonic seizures. This could affect the external validity of the study.Overall, this study provides valuable insights into the metabolic and systemic

changes associated with TCS. These findings could lead to new diagnostic and treatment strategies for these seizures and related conditions. Further research is needed to confirm this study's findings and investigate the mechanisms underlying the metabolic and systemic changes associated with TCS.Lastly, a holistic clinical assessment encompassing routine blood parameters is advised to capture the broader systemic effects of TCS, guiding a more comprehensive approach to patient care.

CONCLUSION

Our comprehensive study uncovered the significant impact of tonic-clonic seizures (TCS) on a wide range of metabolic processes throughout the body. The study underscores the significance of monitoring lactate and ammonia levels during TCS episodes as valuable indicators of seizure severity and metabolic disturbances. This study highlighted a substantial elevation in lactate levels among individuals experiencing tonic-clonic seizures. Furthermore, this observation revealed markedly elevated ammonia levels in the case group, attributable to heightened muscle activity during seizures, resulting in ammonia release into the bloodstream.

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