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Evaluation of Cardiac Troponin Level Following Generalized Tonic-Clonic Seizure in Children; Cross-sectional Study

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Abstract

Background: Cardiac troponin I (CTnI) is recognized as a proper marker for early detection of cardiac damage. Generalized tonic-clonic (GTC) seizures may lead to cardiac ischemia or myocardial injury associated with elevated CTnI. The present study aimed at evaluating the level of CTnI in children with status GTC seizures.
Methods: 50 patients with GTC seizures and a normal cardiac function referred to Amirkabir Hospital, Arak, Iran were evaluated. The medical history of all patients was taken, and clinical examinations were performed. For all patients were performed Serum CTnI measurements, electroencephalography (EEG), electrocardiography (ECG), and echocardiography.
Results: The patients' mean age was 7.80 ± 4.01 years and 26 (52%) children were female (female: male ratio, 1.08). the mean duration of seizure was 31.54 ± 1.56 minutes. Abnormal EEG patterns were documented in 83 (86%) patients, while abnormal CT scan was not found in any of the patients. The mean level of CTnI was at the high end of the range in patients (57.02 ± 10.80 ng/mL). There was a positive correlation between serum CTnI and age (P = 0.001, R = 0.492). Also, the serum level of CTnI was significantly correlated with the onset of GTC seizure (R = 0.004, P = 0.001).
Conclusion: The serum CTnI level exceeded the normal level in children with seizures. Therefore, cardiac monitoring of patients with status GTC seizures may be helpful in the ictal and postictal phases for evaluating cardiac injury, especially in children with risk factors for coronary diseases, such as Kawasaki disease, cardiomyopathy, or coronary anomalies.

Keywords: Cardiac Troponin I, Children, Epilepsy, Myocardial Injury, Seizure

1. Background

Epilepsy, as a common neurological disorder in the pediatric population, is associated with recurrent seizures. Status generalized tonic-clonic (GTC) seizure is a prevalent neurological disorder in children. Cardiac troponin I (CTnI) is identified as a specific and sensitive marker for cardiac tissue injury. According to previous studies, ischemic cardiac injury results in the release of CTnI into the blood circulatory system; however, seizure itself may not be responsible for the increased level of troponins.

In epileptic patients, if the level of cardiac troponins exceeds the recommended limit, the risk of an ischemic cardiac event increases. On the other hand, in seizure patients with elevated CTnI, events, such as subdural hematoma, subarachnoid hemorrhage, and brain stroke, should be taken into consideration (1). Nevertheless, previous studies on adults have reported contradictory findings regarding the serum level of CTnI in patients with seizures. In some studies, patients with acute neurological diseases, such as rare GTC seizures, showed an increase in the troponin content (2-4).

Some researchers believe that an increase in troponin level after a GTC seizure arises from the release of unbound cytosolic troponins due to the increased permeability of myocardial cell membranes and damage to myocytes (5), while others believe that an increase in the troponin content suggests a transient myocardial injury (6). In this regard, another study suggested that the increased level of CTnI could be a risk factor for GTC seizures in children (7).

2. Objectives

The present study aimed at evaluating the role of CTnI as a biomarker for cardiac injury in children with GTC seizures.

3. Methods

This study evaluated 50 patients with status GTC seizures from January 2017 to June 2018 referred to Amirkabir Hospital, Arak, Iran. The sample size was calculated based on similar study and with considered prevalence of GTC seizures equal to 76% (8) with following formula:

$$n = \frac{Z^2_{1-\frac{\alpha}{2}} \times P\,(1-P)}{(0.16 \times P)^2}$$

$$n = \frac{2^2 \times 0.76 \times 0.24}{(0.16 \times 0.76)^2}$$

$$n = 50$$

Informed consents were collected from the neonates' parents, as well as adolescent patients before the study. The ethics committee approved this study (IR.ARAKMU.REC.1396.190).

Epilepsy was diagnosed based on the clinical examinations, electroencephalography (EEG), and medical history. The exclusion criteria were as follows: 1- diagnosis of myocarditis; 2- history of cardiac anomalies or other diseases affecting the autonomic nervous system or cardiovascular system; and 3- regular use of medications (except antiepileptic drugs) in acute cases with possible effects on the cardiovascular system or autonomic nervous system.

A pediatric cardiologist performed the echocardiography and electrocardiography (ECG). Finally, patients with normal echocardiography and ECG results, without any critical characteristics of cardiac anomalies, were included in the study. On the other hand, patients with abnormal cardiac echocardiography or ECG findings were excluded. Careful history-taking (e.g., age, gender, and neurological history) was performed for all patients, with an emphasis on convulsion (e.g., onset, course, frequency, severity, and duration of disease), duration and dose of drug treatment, intake frequency, and family history of epilepsy. The general appearance and respiration of patients were also analyzed, in addition to cardiac analysis and full neurological examination.

Awake or sleep EEG was carried out for all participants. In addition, brain MRI or CT scan was performed to evaluate seizures. Blood samples (3 mL) were collected from each patient for measuring the level of CTnI using an ELISA assay. The normal serum level of CTnI is zero, although concentrations up to 2 ng/mL are also considered in the normal range and unrelated to ischemia or injury. The CTnI level was higher than 100 ng/mL as in patients with ischemic injuries or cardiac injuries with necrosis. Generally, a CTnI level of 2 - 100 ng/mL characterizes a cardiac injury without necrosis or acute ischemia. The CTnI level was measured upon admission or after seizure onset, as well as 6, 12, and 18 hours after admission. Serum electrolytes, including sodium, potassium, calcium, phosphorus, and magnesium, were also measured in the first blood samples. If the patient had abnormal serum electrolytes, he/she was eliminated.

3.1. Statistical Analysis

Data are presented as percentages for categorical variables and mean ± SD for quantitative variables. SPSS v. 23 (SPSS Inc., USA) was used for data analysis. The Kolmogorov Smirnov was performed to assessing the normality distribution. All variable had a normal distribution, so, the Pearson's correlation coefficient test was performed to assess the relationship between CTnI level and other parameters. The significance level was set at $P < 0.05$.

4. Results

Fifty patients with status GTC seizures and a normal cardiac function were examined in this study. Overall, 24 (48%) and 26 (52%) patients were male and female, respectively. The patients' mean age was 7.80 ± 4.01 month (range, 1 month to 14 years) (Table 1). Also, the results of Kolmogorov Smirnov shows that the distribution of data were normal ($P > 0.05$).

The ECG and echocardiography findings were normal in patients, thereby ruling out cardiomyopathy, arrhythmia, and channelopathies. In all patients, the serum level of CTnI was at the high end of the range. Table 2 presents the CTnI levels, while Table 3 indicates the lipid profile and serum electrolytes. No other cardiac etiology was found to be associated with the elevated CTnI, and no hemorrhagic complications or lesions were detected in brain imaging. The CTnI level was positively correlated with age ($P = 0.001$, $R = 0.492$), while there was no significant correlation between CTnI and gender. The EEG findings of all groups showed 43 (86%) abnormal cases.

All patients were idiopathic, without a secondary etiology. CT scan or MRI was performed for all patients. Abnormal CT scan findings were not reported in any of the patients. The patients had higher levels of troponin (57.02 ± 10.80 ng/mL). The findings showed that the serum level of CTnI had a significant positive correlation with the duration of status GTC seizure ($R = 0.52$, $P = 0.001$), and a negative correlation with age ($R = -0.47$, $P = 0.001$).

5. Discussion

CTnI is recognized as a specific and sensitive marker for cardiac tissue injury. However, an increase in the

Table 1. Demographic Characteristics of Patients with Epileptic Seizures

	Mean	SD	Min	Max
Age (mo)	7.80	4.01	1	168
Elapsed time from the last seizure (mo)	11.68	8.99	1	29
Elapsed time from the onset of seizure (min)	31.54	1.56	20	35
Age at first seizure (mo)	4.12	3.35	1	142
CTnI level (ng/mL)	57.02	10.80	12	83
SBP	91.72	17.34	75	140
DBP	58.13	13.77	48	80
Hb	12.84	2.12	9.2	16.23
Lactic acidosis	7.21	0.28	7.11	7.31

Abbreviations: CTnI, cardiac troponin I; DBP, diastolic blood pressure; SBP, systolic blood pressure; Hb, hemoglobin.

Table 2. CTnI Level in Different Intervals from the Onset of Seizure in Patients

	Mean	SD	Max	Min
CTnI after onset	30.80	5.98	40	20
CTnI after 6 hours	48.12	3.62	55	41
CTnI after 12 hours	40.68	5.91	50	32
CTnI after 18 hours	21.42	5.59	30	13

Abbreviation: CTnI, Cardiac Troponin I.

Table 3. Blood Serum Analysis in Patients with Epileptic Seizures

	Mean	SD	Max	Min
BS	103	49	120	40
Cr (mg/dL)	0.50	0.13	0.70	0.30
BUN	13.88	4.90	20	5.2
HDL	49.70	3.16	55	45
LDL	100.60	8.90	114	80
TG	81.54	4.62	93	75
Chl	152.70	12.00	171	89
Ca	9.38	0.61	10.50	8.50
K (mg/dL)	4.42	0.63	5.50	3.50
Na	139.68	3.11	145	135
Mg	1.92	0.13	2.10	1.70
P	4.85	0.34	5.40	4.30

Abbreviations: BS, blood sugar; Cr, creatinine; BUN, blood urine nitrogen; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Chl, cholesterol; Ca, calcium; TG, triglyceride; K, potassium; Na, sodium; Mg, magnesium; P, phosphorus.

plasma level of CTnI seems to be associated with several non-ischemic cardiac anomalies (e.g., myocarditis and cardiomyopathy), as well as non-cardiac disorders (e.g., subdural hematoma, brain stroke, subarachnoid hemorrhage, and septicemia).

Myocardial injury associated with seizure is not unexpected, considering the increased myocardial oxygen consumption, tachycardia, apnea, and excess catecholamine release, all of which may lead to myocardial injury. Based on our findings, the mean serum level of troponin exceeded the normal range in seizure patients; however, the troponin level did not surpass the ischemic range, as indi-

cated in a previous study (9).

Some studies have revealed that an increase in the level of CTnI suggests myocardial injury in many patients with seizure-related problems, such as subdural hematoma, severe head injury, subarachnoid hemorrhage, and stroke (10). In some other studies, the increased level of CTnI was found to be associated with diseases, including cardiac amyloidosis, pheochromocytoma, massive pulmonary emboli, and carcinoid syndrome (11-14). The rise in CTnI level due to neurological conditions seems to cause unfavorable changes, which may be associated with cardiac comorbidities (10, 14). Overall, patients should be evaluated for other factors, such as metabolic acidosis, which may result in cardiac tissue injury in case of seizure.

In prolonged seizures, lactic acidosis occurs due to generalized seizure or respiratory acidosis, increasing the patient's susceptibility to hypotension and cardiac arrhythmia (11-13). Two important mechanisms may be involved in myocardial cell injury in relation to seizures:

1- GTC seizure triggers severe physical activities, while skeletal muscle contraction increases the cardiac afterload in the tonic stage, leading to a transient imbalance in the cardiac tissue demand, which is associated with myocardial cell damage.

2- Neural-hormonal factors contribute to myocardial cell damage (e.g., brain hemorrhage and brain stroke). The imbalance of autonomic nervous system increases in the sympathetic nervous system, and significant release of catecholamine in blood during seizure can damage cardiac tissues. The increased myocardial wall tension, besides neural-hormonal stress, leads to troponin release associated with cardiac cell wall damage (6). In the present study, this mechanism had greater effects on myocardial tissue damage due to hypoxia in seizures.

EEG, as a cost-effective and convenient tool, is important in both management and diagnosis of seizure-related disorders, as it can indicate abnormal cortical excitability due to epilepsy. On the other hand, since 10% of patients with epilepsy do not have epileptiform discharges, normal EEG cannot be used to exclude epilepsy. Considering the intermittent and unpredictable nature of epilepsy, most EEGs are performed between seizure attacks, not during attacks. In our study, the EEG findings indicated 33 (86%) abnormal cases in all groups.

In a study by Andrade et al., interracial recordings were normal in nearly 40% of patients, and it was claimed that normal EEG cannot exclude epilepsy (15). Similarly, Hajsadeghi et al. showed that CTnI level did not exceed the normal range in two groups of evaluated patients, although patients with complicated seizures showed significantly higher levels of CTnI in comparison with the uncomplicated group (9). Moreover, in the study by Del Rey et al., the higher level of CTnI was attributed to the negligible cardiac tissue damage during seizures in complicated patients (16).

Colugnati DB et al. reported an increase in CTnI level in nearly 30% and 83.3% of patients with uncomplicated and complicated epilepsy, respectively (17). In addition, in a study by Chaiworapongsa et al., the level of CTnI increased marginally in newborns of preeclamptic mothers; this finding was attributed to a mild myocardial damage (18). Moreover, Attia Khattab AA et al. reported the greatest increase of CTnI in the complicated epilepsy group, followed by the uncomplicated epilepsy and control groups. They indicated a direct association between the level of CTnI and mental retardation, prenatal problems, abnormal CT or MRI findings, and EEG abnormalities. Additionally, an indirect correlation was found between the onset age of seizure and CTnI level (7).

It can be concluded that an increase in the level of troponin may occur due to cardiac tissue injury, without necrosis or non-acute ischemia. It is also an important risk factor for multiple diseases, including Kawasaki disease, coronary artery disorders, cardiomyopathy, and cardiac ischemia.

5.1. Conclusion

The higher level of troponin in patients with GTC seizures may be associated with negligible cardiac tissue injury, which results in the serum troponin release by increasing the cardiac cell membrane permeability. In future studies, cardiac monitoring of status GTC seizures in the ictal and postictal phases is necessary, based on the repeated measurement of CTnI after seizure. Regular follow-ups with CTnI measurements are also recommended for early diagnosis of cardiac ischemia, particularly in association with severe neurological deficits.

5.2. Limitations

The relatively low sample size is a potential limitation of this study. Also, neonatal and pediatric problems in patients with elevated CTnI were not evaluated, and the correlation between elevated CTnI and etiology of seizure remains to be elucidated.

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Footnotes

Authors' Contribution: Ghandi Y, proposed the main concept and idea of the research, performed the research and wrote the paper; Shariatmadari F, Data collection; Habibi D, Statistical analysis and interpretation data. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.Shariatmadari F, Data collection; Habibi D, Statistical analysis and interpretation data. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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