Characteristics and treatments of patients with significantly elevated creatine kinase levels induced by seizures: case report and literature review

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ABSTRACT

Background: Motor signs accompanying seizures have been considered to result in over-exertion of muscles and have the ability to cause elevated levels of serum creatine kinase (CK). There were no previous studies on the treatment of seizure-induced elevated CK. We summarized the characteristics and treatments of six patients with significant elevation of CK after seizure onset.

Case report: There were four males and two females, the age range was 16 to 68 years. The CK levels were greater than 5,000 U/L in five of the six patients and the highest CK level was 39,300 U/L. All patients exhibited an estimated glomerular filtration rate (eGFR) < 90 ml/min/1.73m^2. No patient developed renal failure or required continuous renal replacement therapy. We determined that serial assessment of CK, myoglobin, eGFR, and electrolytes should be performed in patients following seizures. Furthermore, fluid resuscitation, urine alkalization, and diuretic agents should be administrated when CK are significantly elevated after seizure onset.

Conclusions: Serial assessment of CK levels after seizures should be performed, especially when the patient experiences electrolyte disorders. Fluid resuscitation, urine alkalization, and diuretic agents also should be administrated to patients when they exhibit a significantly elevated CK or myoglobin after seizures.

Keywords: Creatine kinase, Seizures, HyperCKemia, Acute kidney injury, Treatment

Background

Elevated serum creatine kinase (CK) could indicate muscle cell damage due to muscle trauma, strenuous exercise, or the use of certain drugs [1-3]. Numerous cytoplasmic components within muscle cells exit through the damaged sarcolemma, including myoglobin and electrolytes, which are involved in acute kidney injury (AKI) and possible cardiac dysrhythmia [1, 4, 5].

Motor signs associated with seizures, including tonic, clonic, and myoclonic movements, can be considered muscle overuse [1, 6]. Seizures can induce elevated CK levels, which might serve as a marker to distinguish epileptic seizures from non-epileptic seizures [7-10]. Seizures have been identified as the cause of 4.0% of the cases of rhabdomyolysis (RM) and 6.1% of the exertional RM cases [11, 12]. One study demonstrated that renal replacement therapy or in-hospital mortality due to seizures accounted for 6.0% of patients with CK $>$ 5,000 U/L [13]. Elevated CK levels induced by seizures have been observed in clinical practice, but the occurrence has not received much attention, and there are few published reports on this topic. Given that CK levels can be elevated when seizures occur, this could lead to severe complications. Therefore, appropriate treatment should be provided that might improve the prognosis of patients with seizure onset.

However, rare cases of significantly elevated CK caused by seizures were reported in clinical practice, and there were no previous studies on the treatment of seizures induced elevated CK. In this study, we summarized the characteristics and treatments of six patients with significantly elevated CK levels induced by seizures. We anticipated that the results reported here would encourage more attention to this infrequent complication associated with seizures.

Case Report

From January 2022 to January 2023, we observed six patients who experienced significant CK elevations after seizure onset. Five patients exhibited CK $>$ 5,000 U/L within three days after admission. As shown in Table 1 (Part I), there were four males and two females, and the age range was 16 to 68 years. Only patient 6 was currently consuming alcohol. Concerning the patients' disease history, three patients had hypertension, and one patient had autoimmune encephalitis. The other patients did not have any history of prior major disease. All patients had no history of statin usage. The patients also did not exhibit any significant fever, hyperventilation, tachycardia, or hyperpiesia at admission.

The patients' seizure histories are shown in Table 2. Patient 2 had been diagnosed with epilepsy for six months, and he had been taking sodium valproate. Four patients had probable provoked indications before seizures [14], including bowel preparations, vaccination, vomiting, or diarrhea. Based on the diagnostic criteria for seizures proposed by the International League Against Epilepsy [6], motor signs were described as tonic or tonic-clonic in two patients. The seizures were described as "convulsions" in the other patients, as medical history providers could not describe "tonic," "clonic," or "myoclonic" precisely. All patients displayed impaired awareness during their seizures, and four had recurring seizures. However, only patient 4 had a recurrence with impaired interictal awareness. The seizure duration for all patients was a maximum of five minutes. No epileptiform discharges were observed on video electroencephalogram (VEEG) after admission for any of the patients. Magnetic resonance imaging indicated that only patient 2 exhibited a brain lesion in the left frontal lobe that was a probable epileptic focus [14].

We summarized the results from the laboratory tests for CK, myoglobin, electrolytes, and the estimated glomerular filtration rate (eGFR) because we focused on the seizure-induced elevation of CK and its complications. The interval between the first onset to admission (IT) ranged from one to three days. As shown in Table 1 (Part II) and Figure 1, the CK levels increased gradually starting on the first day, peaked at three to five days, and decreased significantly at six to seven days. The CK levels may return to normal ten days after seizures. The level of CK was greater than 5,000 U/L in five of the six patients and the highest CK level was 39,300 U/L in patient 2. Significantly elevated myoglobin (4,194 μg/L) was observed in patient 5. However, there was no positive correlation between the elevated CK and myoglobin. The eGFR was calculated using an equation validated in the Chinese population [15]. Three patients exhibited an eGFR $<$ 90 ml/min/1.73m^2 and one patient had an eGFR $<$ 60 ml/min/1.73m^2 on admission. There were several significant electrolyte disorders in patients 4 and 6, who had hyponatremia, hypokalemia, or

hypomagnesemia.

The treatment protocols are presented in Table 3. We used conservative measures to prevent AKI, which might be induced by muscle damage, including fluid resuscitation, urine alkalization, and diuretic agents. The CK levels in all patients decreased significantly during treatment after admission, and they exhibited a higher eGFR at discharge compared to their eGFR at admission.

Discussion

Seizures have the ability to increase CK levels and even increase the rate of in-hospital mortality [2, 12, 13]. Bosch et al. proposed that less severe RM with few symptoms and no renal failure could be designated hyperCKemia [2]. No patient developed renal failure or needed renal replacement therapy in the present study. Therefore, in this study, it was appropriate to define elevated CK as hyperCKemia.

In the current study, patients did not experience any trauma, metabolic disorders, alcohol abuse, exposure to drugs or toxins, infection or sepsis, myocardial infarction, or other diseases associated with hyperCKemia [2, 7]. However, significant electrolyte disorders caused by bowel preparation, vomiting, and diarrhea were observed in patient 4 (hyponatremia and hypomagnesemia) and patient 6 (hypokalemia and hypomagnesemia). Among the different electrolyte disorders, hypokalemia and hypophosphatemia are known to cause damage to myocytes [1], but hypophosphatemia was not observed in our cases.

Some studies indicated that a potassium level less than 2.0 mmol/L observed in the initial evaluation could potentially cause RM [1, 16-18]. In the present study, it appeared that hypokalemia was not the primary cause of hyperCKemia in patient 6, who exhibited a potassium level of 2.66 mmol/L. No causal association has been established between desmopressin acetate-induced hyponatremia and muscle injury in animal studies [19]. In a clinical study, asymptomatic hyperCKemia was associated with hyponatremia caused by diuretics and polydipsia, which may have been complicated by AKI [20]. Compared to ultra-athletes with normonatremia, exercise-associated hyponatremia is prone to develop into exercise-associated RM [21]. Severe hyponatremia was observed in patient 6, and we considered that hyponatremia might promote the development of hyperCKemia. Hypomagnesemia was observed in two patients, which may have been due to gastrointestinal losses as they had a history of bowel preparation, vomiting, and diarrhea [22]. There was less possibility of other causes of hypomagnesemia because these patients did not have any history of hypomagnesemia, and their serum magnesium gradually recovered after supplementation. Therefore, for these two patients, hyperCKemia might have been caused synergistically by electrolyte disorders and seizures.

Consequently, it was likely that the seizures experienced by the patients in the present study caused the hyperCKemia. Other factors might have been involved in the pathophysiological process associated with muscle damage, especially the electrolyte disorders. Thus, we recommend performing serial testing for levels of CK and electrolytes after seizure onset.

Early and aggressive repletion of several liters of fluid to restore renal perfusion and increase the urine flow rate is the primary management for AKI [1, 2, 23]. We administered normal saline at 1,500 ml/day to the majority of patients with kidney function impairment in the cases in this study. Fluid was administered at a rate of 2,500 ml/day to patient 6 due to his history of vomiting and diarrhea. Only patient 6 had a lower eGFR (55.65 ml/min/1.73m^2). However, patient 6 did not report any history of kidney function impairment, such as renal disease, toxin exposure, or sepsis [24]. Unfortunately, we could not investigate the reason for this outcome, as patient 6 did not have a follow-up examination.

Urinary alkalization and diuretic agents were administrated to the patients in this study. Alkaline urine might prevent lipid peroxidation, redox-cycling, and myoglobin cast formation [2, 23]. Diuresis might prevent the accumulation of debris in the renal tubules, increase renal perfusion, and improve myoglobin excretion [1, 24]. Mannitol should be avoided in anuric patients, and electrolytes should be monitored if loop diuretics are used [1, 25]. Fortunately, no patient in this study developed renal failure or required continuous renal replacement therapy, probably due to the rate for renal failure was lower in exertional RM or generalized tonic-clonic seizures [10, 12]. The eGFR for all patients increased after treatment even though the recovery

level was less than 90 mL/min/1.73m^2 at the time of discharge. It might be necessary to conduct a follow-up examination.

Conclusions

Seizures have the ability to induce hyperCKemia and even cause RM. Therefore, serial assessment of CK levels after seizures should be performed, especially when the patient experiences electrolyte disorders. Monitoring eGFR, electrolytes, and electrocardiography should be performed in patients who exhibit hyperCKemia after seizures. Fluid resuscitation, urine alkalization, and diuretic agents also should be administrated to patients when they exhibit a significantly elevated CK or myoglobin after seizures.

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Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Anhui Medical University (Hefei, China).Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Data availability statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Author Contributions

WK and YJW conceptualized the work, collected the data, analyzed the data and drafted the initial manuscript. WL and XWH collected the data, analyzed the data, reviewed and revised the manuscript. WY conceptualized and organized the work, reviewed and revised the manuscript.

Competing interests

The authors declare that this article content has no competing interests.

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