Factitiously Low Total Creatine Kinase Activity in Severe Rhabdomyolysis: A Case Series

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Received February 4, 2025; Accepted August 27, 2025.

Key words: Creatine kinase – Rhabdomyolysis – Analytical interference – Clinical chemistry – Laboratory medicine

Abstract: Factitiously low total creatine kinase (CK) activity can occur in severe rhabdomyolysis, potentially causing misdiagnosis and inappropriate patient management. We hereby describe 2 cases of severe rhabdomyolysis with falsely low total CK activity. Case 1 was a 61-year-old lady with underlying diabetes mellitus diagnosed with severe rhabdomyolysis secondary to severe pneumonia. Case 2 was a 77-year-old man with underlying diabetes mellitus diagnosed with severe rhabdomyolysis secondary to recurrent pyogenic spondylodiscitis. Both cases showed unexpectedly low total CK activity (<7 U/l N: 26–192 U/l). Post-dilution procedures showed markedly elevated total CK activity for case 1 (18,364 U/l [1:11]) and case 2 (15,217 U/l [1:11]). Unfortunately, both patients succumbed despite optimized medical treatment due to multi-organ failures. Measurement of CK in blood is considered as a diagnostic marker for rhabdomyolysis and its severity. Most of the laboratory nowadays measures total CK activity using enzymatic coupled with spectrophotometry method. However, substrate depletion can occur in severe rhabdomyolysis in which creatine phosphate is consumed by high concentration of CK in sample before the kinetic measurement is initiated, leading to factitiously low total CK activity. Sample dilution can be done to obtain the accurate total CK activity, avoiding result reporting error and possibility misdiagnosis of rhabdomyolysis. Good communication between clinical and laboratory personnel is vital to prevent the error and safeguard patient management.

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https://doi.org/10.14712/23362936.2025.26
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Introduction

Rhabdomyolysis is a medical condition associated with rapid dissolution of damaged skeletal muscle (Torres et al., 2015). Measurement of creatine kinase (CK) in blood is considered as a diagnostic marker for rhabdomyolysis and its severity as disruption of skeletal muscle integrity leads to the release of CK as part of intracellular muscle components as well as myoglobin, lactate dehydrogenase and electrolytes into bloodstream (Nance and Mammen, 2015; Torres et al., 2015). Although rhabdomyolysis is most commonly caused by direct traumatic injury, uncommonly it can be secondary to severe infections (Torres et al., 2015; Zhao and Zheng, 2019). Postulated mechanisms for rhabdomyolysis secondary to infection include tissue hypoxia due to sepsis, dehydration, toxin, direct invasion by microorganisms, pyrexia associated or rigors (Torres et al., 2015).

Case report

Case 1

A 61-year-old Malay lady with underlying diabetes mellitus presented with productive cough associated with shortness of breath for 3 days. No chest pain, no history of contact with sick individual, no history of traveling and no history of trauma. Upon arrival at the emergency department she was alert, conscious,

Table 1: Case 1 laboratory investigations

Test		Result	Unit	Reference range
Complete full blood count	WBC	18.1×10^9	/l	4.38–10.00
	RBC	5.07×10^9	/l	3.91–5.30
	Hb	11.6	g/dl	11.24–15.07
	Hct	35.5	%	33.80–45.22
	MCV	69.4	fl	78.03–94.96
	MCH	27.2	pg	24.45–31.49
	MCHC	32.4	g/dl	30.65–33.75
	Plt	219×10^9	/l	198–405
Coagulation profile	PT	13.7	s	12.61–15.72
	INR	1.0		0.86–1.14
	APTT	41.8	s	30.00–45.80
Liver function tests profile	Total protein	50	g/l	66–87
	Albumin	24	g/l	39.7–49.4
	AST	1049	U/l	10–35
	ALT	246	U/l	10–35
	ALP	170	U/l	35–104
	Total bilirubin	11	µmol/l	≤ 15
Renal function tests profile	Urea	17.4	mmol/l	2.76–8.07
	Sodium	138.0	mmol/l	136–145
	Potassium	6.1	mmol/l	3.5–5.1
	Chloride	98.0	mmol/l	98–107
	Creatinine	601.0	µmol/l	44–80
Creatine kinase		< 7	U/l	26–192
		18364 (post dilution 1:11)		
		306.68 (post dilution 1:11)	µkat/l	0.43–3.21
LDH		367	U/l	135–214
Urinalysis (dipstick)	Leukocytes	negative		negative
	Nitrite	negative		negative
	Urobilinogen	normal		normal
	Protein	negative		negative
	pH	5.1		4.7–7.8
	Red blood cell	negative		negative
	SG	1.007		1.005–1.030
	Ketone	negative		negative
	Bilirubin	negative		negative
	Glucose	negative		negative

WBC – white blood cells; RBC – red blood cells; Hb – haemoglobin; Hct – haematocrit; MCV – mean corpuscular volume; MCH – mean corpuscular haemoglobin; MCHC – mean corpuscular haemoglobin concentration; Plt – platelet; PT – prothrombin time; INR – international normalized ratio; APTT – activated partial thromboplastin time; AST – aspartate aminotransferase; ALT – alanine aminotransferase; ALP – alkaline phosphatase; LDH – lactate dehydrogenase; SG – specific gravity

Prague Medical Report / Vol. 126 (2025) No. 3, p. 162–166

pink, tachypneic and lethargic looking. Her vital signs were as followed: blood pressure of 89/70 mm Hg, pulse rate of 113 beats/min, respiratory rate of 32 breaths/min, temperature of 37 °C and oxygen saturation of 55% under room air. Respiratory examinations showed coarse crepitation on right side of the lung. Other systematic examinations showed no significant findings. She was intubated due to severe hypoxia and started on inotropic supports due to haemodynamically unstable. She was diagnosed with septicaemic shock secondary to severe community acquired pneumonia and admitted to intensive care unit (ICU) for further management and monitoring. While in the ICU she became oliguric and passed out brownish coloured urine. Thus, the diagnosis of myoglobinuria secondary to rhabdomyolysis was considered. However, her total CK activity showed persistently very low results despite samples were repeated 12 hours apart, prompting the treating clinician to contact laboratory. Sample dilution was done and post-dilution procedures showed markedly elevated total CK activity. The samples were not diluted, not haemolysed, not icteric and not lipaemic. No other CK samples of different patients showed similar very low results on the same day of testing. Her renal and liver profiles showed features of acute kidney injury and liver impairment, respectively. Urine myoglobin was not offered by our laboratory. Her final diagnosis was severe rhabdomyolysis secondary to severe pneumonia. Unfortunately, her conditions worsened and she succumbed despite optimized medical treatment due to multi-organ failures. Her laboratory results were summarized in Table 1.

Case 2

A 77-year-old Malay man with underlying diabetes mellitus and recurrent L4-L5 pyogenic spondylodiscitis presented with fever associated with back pain and spasm for 4 days. No cough, no abdominal pain, no vomiting, no loose stool, no history of contact with sick individual, no history of traveling and no history of trauma. Upon arrival at the emergency department he was alert, conscious, pink and lethargic looking. His vital signs were as followed: blood pressure of 85/79 mm Hg, pulse rate of 110 beats/min, respiratory rate of 17 breaths/min and temperature of 38 °C. Examination at the back showed tenderness

Table 2: Case 2 laboratory investigations

Test		Result	Unit	Reference range
Complete full blood count	WBC	15.3×10^9	/l	4.68–9.70
	RBC	5.07×10^9	/l	4.43–6.09
	Hb	14.00	g/dl	13.0–16.8
	Hct	42.50	%	40.14–51.77
	MCV	80.40	fl	79.10–94.70
	MCH	29.70	pg	24.81–31.10
	MCHC	31.70	g/dl	30.52–33.97
	Plt	203×10^9	/l	169–372
Coagulation profile	PT	12.70	s	12.61–15.72
	INR	1.03		0.86–1.14
	APTT	39.80	s	30.0–45.8
Liver function tests profile	Total protein	48	g/l	66–87
	Albumin	25	g/l	39.7–49.4
	AST	1379	U/l	10–50
	ALT	285	U/l	10–50
	ALP	73	U/l	40–129
	Total bilirubin	17	µmol/l	≤ 24
Renal function tests profile	Urea	24.1	mmol/l	2.76–8.07
	Sodium	139.0	mmol/l	136–145
	Potassium	5.4	mmol/l	3.5–5.1
	Chloride	105.0	mmol/l	98–107
	Creatinine	427.0	µmol/l	62–106
Creatine kinase		< 7	U/l	39–308
		15217 (post dilution 1:11)		
		254.12 (post dilution 1:11)	µkat/l	0.43–3.21
LDH		348	U/l	135–225

WBC – white blood cells; RBC – red blood cells; Hb – haemoglobin; Hct – haematocrit; MCV – mean corpuscular volume; MCH – mean corpuscular haemoglobin; MCHC – mean corpuscular haemoglobin concentration; Plt – platelet; PT – prothrombin time; INR – international normalized ratio; APTT – activated partial thromboplastin time; AST – aspartate aminotransferase; ALT – alanine aminotransferase; ALP – alkaline phosphatase; LDH – lactate dehydrogenase

at L4-L5 region with no wound and neurological deficit. Other systematic examinations showed no significant findings. He was started on inotropic supports due to haemodynamically unstable. He was diagnosed with septicaemic shock secondary to possible recurrent L4-L5 pyogenic spondylodiscitis and admitted to ICU for further management and monitoring. While in the ICU he complained of intense muscle spasm and pain thus, the diagnosis of rhabdomyolysis was considered. He also became oliguric. Nevertheless, his total CK activity showed persistently very low results despite samples were repeated 12 hours apart, prompting the treating clinician to contact laboratory. Sample dilution was done and post-dilution procedures showed markedly elevated total CK activity. The samples were not diluted, not haemolysed, not icteric and not lipaemic. No other CK samples of different patients showed similar very low results on the same day of testing. His renal and liver profiles showed features of acute kidney injury and liver impairment, respectively. Magnetic resonance image (MRI) of spine was done and confirmed the diagnosis of pyogenic spondylodiscitis. His final diagnosis was severe rhabdomyolysis secondary to recurrent pyogenic spondylodiscitis. Unfortunately, his conditions worsened and he succumbed despite optimized medical treatment due to multi-organ failures. His laboratory results were summarized in Table 2.

Discussion

These 2 cases illustrated the falsely low total CK activity in severe rhabdomyolysis. Total CK is the most sensitive marker for myocyte injury (Nanda et al., 2016). A 5-fold increase of total CK activity from normal level is diagnostic of rhabdomyolysis and its activity is directly proportional to the degree of muscle injury (Nanda et al., 2016).

There are different causes to be considered for falsely low total CK activity in rhabdomyolysis which can be classified into errors in pre-analytical, analytical and post-analytical (Nanda et al., 2016). Pre-analytical errors accounted for 32 to 75% of total errors followed by analytical 13 to 32 % and post-analytical 13 to 40% (Nanda et al., 2016). Although pre-analytical errors are more frequent, analytical errors could lead to more severe consequences for patient management (Nanda et al., 2016).

Pre-analytical errors include wrong patient identification, insufficient sample volume, diluted sample and wrong timing of measurement. Diluted sample can cause dilutional effect as in aggressive fluid resuscitation which can dilute CK activity leading to falsely low total CK activity. Diluted sample is usually indicated by hyponatremia and low urea which were not present in both cases. Correct timing of measurement is important as CK activity rises within 2–12 hours, peaked in 3–5 days and started to decline in 6–10 days after the onset of muscle injury (Nance and Mammen, 2015). Measuring CK too early or late from this window period may result in falsely low activity. Both the cases had CK samples repeated within 12 hours apart and yet the results still persistently very low thus, eliminating wrong timing of measurement as the causing factor.

Analytical errors include interferences in method measurement, faulty calibration and internal quality control and malfunctioning instrument. Most of the laboratory nowadays measures total CK activity using enzymatic coupled with spectrophotometry method (Lopez et al., 2012). Creatine phosphate and adenosine diphosphate (ADP) serve as substrates and CK will catalyse these substrates, triggering subsequent reactions leading to formation of nicotinamide adenine dinucleotide phosphate (NADPH) which can be measured spectrophotometrically through absorbance at wavelength 340 nm (Lopez et al., 2012; Pant, 2022). The rate of increase in NADPH absorbance is directly proportional to the CK activity present in serum (Lopez et al., 2012; Pant, 2022). Total CK activity of both cases were analysed by Roche Cobas c503 chemistry analyser. In severe rhabdomyolysis, interference can occur as creatine phosphate is consumed by high concentration of CK causing substrate exhaustion before the kinetic measurement is initiated, leading to falsely low total CK activity (Nanda et al., 2016). This mechanism is most probable to occur in both cases. The measuring range of the kit used to determine CK is 7–2,000 U/l (0.12–33.4 μkat/l). Dilution of 1:11 as recommended by manufacturer was done for both cases to get the correct values for CK activity. Clinically rhabdomyolysis was suspected by the treating physician and fortunately, both cases were discussed with chemical pathologist. Thus, immediate actions were taken which dilutions of the samples were performed, true results were reported and informed to the physician and appropriate treatment was commenced. Based on the experience by the 2 cases our laboratory had set up automated dilution procedures for CK activity which fall outside the measuring range, updated our laboratory workflow process and provided training for our laboratory staffs regarding this issue to prevent the similar errors from recurring. Other interferences include haemolysed, icteric and lipaemic samples. Bilirubin shows high absorbance at wavelengths 340–500 nm

(Cano-Corres et al., 2023). NADPH absorbance wavelength falls within this range thus, icteric sample may cause spectrophotometric interference leading to falsely low total CK activity. Lipaemic sample also may cause spectrophotometric interference due to light scattering effect, affecting NADPH absorbance and also resulting in falsely low total CK activity (Farrell and Carter, 2016). Haemolysed samples mostly will cause falsely high total CK due to positive interference by enzyme adenylate kinase in red blood cells (Farrell and Carter, 2016). The samples of both cases were not haemolysed, not icteric and not lipaemic as mentioned. Faulty calibration, faulty internal quality control and malfunctioning instrument usually will cause error of measurement in batches of samples not one or two particular sample. This was ruled out in both cases as no other CK samples of different patients showed similar very low results on the same day of testing.

Post-analytical errors include transcription errors especially in manual result entry system, wrong result interpretation, wrong unit conversion, inappropriate sample storage and others. In the current era of automation in clinical laboratory system which include automated result entry, these errors are less probable to occur (Bakan and Bakan, 2021).

In both cases, the results of other tests also supported the diagnosis of rhabdomyolysis. Abnormal liver function tests are commonly seen in severe rhabdomyolysis showing elevation of transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) especially AST as it is also found in skeletal muscle (Lim, 2020). ALT is more liver specific but also found in skeletal muscle in lower concentrations (Lim, 2020). Both cases showed evidence of liver impairment as there were elevation of AST more than 10 times of the upper limit normal (ULN) and elevation of ALT more than 5 times of the ULN. Acute kidney injury (AKI) is one of the most serious complications of rhabdomyolysis (Torres et al., 2015). CK activity of > 5,000 U/l can predict the likelihood of patient developing kidney injury in rhabdomyolysis (Torres et al., 2015). Both cases showed evidence of AKI based on Kidney Disease: Improving Global Outcomes (KDIGO) definition (Makris and Spanou, 2016) as clinically oliguric and elevation of serum creatinine ≥ 1.5 times from baseline (both patients had normal baseline serum creatinine prior the illness). Hypoalbuminemia has been linked to increased morbidity and mortality related to AKI in severe rhabdomyolysis (Wiedermann et al., 2017). Hyperkalaemia and elevated lactate dehydrogenase (LDH) were expected in both cases as potassium and LDH are intracellular analytes which will be released into blood due to myocyte injury in severe rhabdomyolysis.

Conclusion

The low total creatine kinase activity can occur factitiously in severe rhabdomyolysis due to analytical interference of substrate exhaustion in which creatine phosphate is consumed by high concentration of CK in sample before the kinetic measurement is initiated. Sample dilution can be done to obtain the accurate total CK activity, avoiding result reporting error and possibility misdiagnosis of rhabdomyolysis. Good communication between clinical and laboratory personnel is vital to prevent the error and safeguard patient management.

Acknowledgements: Appreciation for the family members of both patients for their consent and cooperation in completing this case report.

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