Low serum creatine kinase activity in hospital patients

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Creatine kinase (CK), an intracellular mitochondrial enzyme present in skeletal and cardiac muscle as well as brain tissue, is responsible for the conversion of creatine to creatine phosphate. This reaction utilises ATP and produces ADP in a reaction that can also be reversed to produce ATP. Creatine phosphate is therefore an important energy reserve in muscle tissues. High plasma CK activities are seen in muscle cell necrosis, inflammation or trauma such as seen in polymyositis, hypothyroidism, extreme exercise and rhabdomyolysis.[1] Low activities of serum CK have earlier been reported in some patients in various short reports in the medical literature.[2–4] However, we wanted to explore the phenomenon of low serum CK activity in a large hospital and general practice population and also relate this to patient outcome such as mortality and length of bed stay.

This study was designed to identify patients tested and treated at a large district general hospital who had subnormal serum CK activities. The frequency of this phenomenon was investigated as well as the potential causes of the low serum CK activities. Understanding the causes for reduced serum CK activity may help the laboratory interpretation of such results.

The serum CK results from patients tested in the biochemistry department of our hospital between 1 October 2012 and 30 September 2013 were examined and any results below 26 IU/L (laboratory reference range 26–180 IU/L) were recorded. Patients with a serum CK result of below 20 IU/L were examined further as this is the lower limit of the lowest reference range reported in the medical literature.[5] Details collected from each patient with a low serum CK activity included age, clinical details, gender and clinical location.

Serum CK was analysed on an Abbott Architect analyser with coefficient of variation (CV%) <5%. As quoted by the manufacturer the assay for CK catalyses the transfer of a high energy phosphate group from creatine phosphate to ADP. The ATP produced in this reaction is subsequently used to phosphorylate glucose to produce glucose-6-phosphate (G-6-P) in the presence of hexokinase. G-6-P is then oxidised by glucose-6-phosphate dehydrogenase with the concomitant reduction of nicotinamide adenine dinucleotide phosphate (NADP) to nicotinamide adenine dinucleotide phosphate reduced (NADPH). The rate of formation of NADPH is monitored at 340 nm and is proportional to the activity of CK in the sample. These reactions occur in the presence of *N*-acetyl-L-cysteine which is present as an enzyme reactivator.

From the laboratory clinical records we determined the causes of reduced serum CK activities and identified patient populations likely to show such results. Data were collected on a Telepath Pathology patient management system. The clinical audit office of our hospital approved this project (Project Number 2729). Ethical committee approval was not required as this was a retrospective observational study. Data were analysed using Microsoft EXCEL statistics software; statistical significance was taken as $P<0.05$.

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Table 1. Age of patients with a serum CK activity <20 IU/L.

Age (years)	Percentage
≥75	52
60-74	21
45-59	14
26-44	9
16-25	5
0-15	0

During the year under investigation, a total of 1422 (6.8% of all CK requests received) samples from 329 patients (3.6%) with a serum CK activity below 26 IU/L were received in the laboratory. 929 (4.2%) samples from 195 (2.2%) patients had a serum CK result of below 20 IU/L. 157 (0.8% of all samples received) samples had a serum CK result below 10 IU/L. 421 samples (2%) had a serum CK between 10 and 15 IU/L. 350 (1.7 %) samples had a serum CK activity between 16 and 19 IU/L.

The vast majority of patients with a serum CK activity below 20 IU/L were elderly above the age of 75 years (Table 1). There was a significantly higher frequency of females than males with a low serum CK activity result (below 20 IU/L; $P<0.05$). A total of 121 females had a serum CK result of <20 IU/L but only 74 males.

The vast majority of patients with low serum CK activity were from acute wards in the hospital (Table 2). The most common locations were the intensive care unit (ITU) and the high dependency unit (HDU).

The association of a low serum CK activity with critical locations in the hospital indicates the potentially serious nature of this biochemical phenomenon. For this reason, the number of patients who had died during their hospital stay in which a low serum CK activity (<20 IU/L) was recorded was investigated. The results showed that 16% of patients had died during their hospital stay.

A low serum CK activity was shown to be associated with a prolonged hospital stay (Table 3). The majority of patients with a serum CK activity value <20 IU/L had a hospital stay of between two weeks and three months.

The clinical details of patients with a serum CK activity below 20 IU/L were available for 66 patients. The potential

Table 2. Location of patients with serum CK activity <20 IU/L.

Hospital location	Percentage
Intensive care unit	52
High-dependency unit	29
Hospital in-patient	12
General practice	2
Accident & emergency	2
Coronary care unit	1

Table 3. Length of hospital stay of patients with low serum CK activity.

Length of hospital stay	Percentage
<1 week	2.7
7–10 days	8.3
10 days–2 weeks	2.7
2 weeks–1 month	38.8
1–2 months	19.4
2–3 months	19.4
3–4 months	5.5
>4 months	2.7

causes of the low serum CK activity were therefore investigated in these patients. The majority of patients were shown to have either pneumonia or renal failure (Table 4).

A low serum CK activity has been shown in this study to be more common in females than males (62 % *vs.* 38 %, $P<0.05$) and is associated with older age (the majority over 75 years). The clinical significance of a low serum CK activity result was shown by the locations of the patients with the majority being located in either the ITU or HDU. The critical nature of such a result is also shown by the high death rate (16%) of patients who have a low CK value. The most common causes of hospitalisation during which a low serum CK is found are shown in Table 4. These results are compatible with previous data.[3–12] Some of these studies relate specifically to patients on ITU but our study was wider and looked at all hospital patients.

Van de Moortel and colleagues reported low serum CK activities are associated with a higher severity of illness and mortality rates in ITU patients.[13] The oxidation of sulfhydryl groups of the CK-M chain due to increased oxidative stress has been suggested as a possible mechanism. Indeed, post-transcriptional modification of creatine kinase in intensive care patients may be important in this context.[14] Our results add to these observations on ITU in that we report low serum CK activity also to be associated with longer hospital stay and also mortality in other patient groups.

It has previously been noted that serum CK activities in patients with multiple organ failure and liver disease can be falsely low due to extracellular glutathione depletion which is not restored by the presence of thiol-reducing compounds in the CK assays.[7] This could indeed be the cause of the low serum CK activity in this group of patients as several of them had liver and multi-organ failure. However, ours was a retrospective review and thus we obviously were unable to measure glutathione in these samples.

Table 4. Clinical details of patients with a low serum CK activity.

Main clinical detail	Percentage
Sepsis including pneumonia	37.9
Renal failure	17
Respiratory failure	10.6
Carcinoma	7.6
Hypertension	6.6
Myocardial infarction	4.5
Diabetes mellitus	4.5
Anaemia	3
Alcoholic hepatitis	3
Head trauma	1.5
Acute pancreatitis	1.5

A low serum CK activity in a patient is therefore a possible warning sign to clinicians to monitor them closely and perhaps instigate treatment regimes in order to improve patient outcomes. A limitation of our study is that it is a retrospective observational study and based upon requesting patterns of clinicians and our findings may merit confirmation in a larger prospective cohort. Our findings may be of use in facilitating laboratory interpretive comments for low serum CK activity results and is one of the few studies that looked specifically at low serum CK activity results in a hospital and general practice population.

In conclusion, we have found the following: a low serum CK activity was more common in females than males (62% *vs.* 38%, $P<0.05$) and was associated with older age (the majority over 75 years). The most common causes of hospitalisation during which a low serum CK activity was recorded were sepsis including pneumonia and renal impairment but also included respiratory failure and cancer. The critical nature of a low serum CK activity result was shown by the locations of the patients with the majority being from either the ITU or HDU and also the high death rate (16%) of patients who have a low CK activity. A low serum CK activity should alert the clinician to potentially serious clinical consequences in their patients. Our novel findings (looking at a large hospital population and also general practice patients) add to the earlier editorial by Rosalki that described causes of low serum CK activity.[15] Understanding the reasons for reduced serum CK activity may allow this to be used as a marker to indicate poor prognosis or as a possible warning sign to initiate emergency treatment in certain patient groups. □

Take home messages:

- Low serum CK activity is rare but is usually found in critically ill patients, such as those on intensive care units.
- Low serum CK activity is more common in females and the elderly.
- Low serum CK activity is associated with long hospital stay and hospital mortality.
- Low serum CK activity is associated with sepsis, organ failure and cancer.

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Bacteraemia caused by *Fusobacterium necrophorum*: a clinical approach to Lemierre's syndrome

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Differential diagnosis can be established by a primary physician through assessment of patient information and presentation. However, it can be hard to discriminate disease entities when symptoms overlap. For example, the differential diagnosis of infective colitis versus other abdominal problems can be complicated. Here, we reported a case of Lemierre's syndrome caused by *Fusobacterium necrophorum*. Characteristically, this case was initially thought to be a common cold with infective viral or bacterial colitis due to diarrhoea symptom. Follow-up study revealed bacteraemia caused by *F. necrophorum*. Lemierre's syndrome can represent septic thrombophlebitis of the internal jugular vein that typically presents as an oropharyngeal infection.[1] This case will help to understand an effective approach for the evaluation of patients with Lemierre's syndrome caused by *F. necrophorum*.

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A 21-year-old Korean man with no history of serious illness was admitted to the emergency room with fever and a sore throat. The fever had begun five days prior and watery diarrhoea three days prior. The patient experienced a high fever (40.5°C), tachycardia (132 beats/min), and tachypnoea (24 breaths/min), and his blood pressure was reported to be 60 to 100 mmHg. Laboratory data at the time of admission were as follows: peripheral white blood cell count was 5900/μL with 97.5% of cells being neutrophils; total bilirubin was increased (2.13 mg/dL); sodium, potassium, and chloride (Na-K-Cl) levels were 127 mmol/L, 3.3 mmol/L, 92 mmol/L, indicating hyponatraemia, hypokalaemia, and hypochloraemia; and erythrocyte sedimentation rate (ESR) was elevated (19 mm/h). Peripheral blood smear analysis revealed relative neutrophilia, toxic change in neutrophilic series, and normocytic normochromic anaemia. Plasma fibrinogen, fibrin degradation product, and D-dimer levels were increased (489 mg/dL, 15.22 μg/mL, and 3.29 μg/mL, respectively). Negative results were reported for the Widal test, hepatitis B surface antigen, hepatitis B surface antibody, anti-hepatitis C virus antibody, human immunodeficiency antigen and antibody, stool white blood cell, *Clostridium difficile* toxin assay, polymerase chain reaction (PCR) for astrovirus, rotavirus, adenovirus, and norovirus from stool specimens, and PCR for influenza A, influenza B, RSV A, RSV B, parainfluenza, coronavirus, rhinovirus, enterovirus, adenovirus, bocavirus, and metapneumovirus from nasal swab specimens. Acute phase indicators, including C-reactive protein, procalcitonin, and ferritin levels, were markedly increased (245.68 mg/L, >100 ng/mL, and 492.20 ng/mL, respectively). Preliminary analysis suggested infective colitis or sepsis. The patient was administered intravenous ceftriaxone (2 g/day for 4 days) and intravenous metronidazole (500 mg*3/day for three days) was added three days after admission. Four days after admission, ciprofloxacin (400 mg/200 mL*2/day) was administered and clindamycin phosphate (600 mg/4 mL*3/day) was added to the regimen six days after admission. Fever subsided to below 38°C. The patient was discharged without critical sequelae 13 days after admission with an eight-day prescription of post-prophylactic amoxicillin plus potassium clavulanate (375 mg*3/day).

Initial chest radiography did not show active lesions in the lungs. However, patchy opacities in the lower part of the lungs indicated the possibility of pneumonia one day after admission. Hepatosplenomegaly and moderate fatty liver were noted on abdominal computed tomography (CT) on the day of admission. Sinus tachycardia and borderline resting pulmonary hypertension were diagnosed using 2D echocardiography and Doppler ultrasound. Three days after admission, chest CT revealed multiple variable-sized nodules with ground-glass halo in both lungs, subsegmental atelectasis in both basal-dependent lungs, and small pleural effusions in both dependent hemithoraces (Fig. 1). Septic