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BRIEF REPORT

Spectrum of rhabdomyolysis in an acute hospital

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Abstract

Rhabdomyolysis is a state of muscle necrosis with the hallmark being elevated creatine kinase that may cause acute kidney injury with serious consequences. It happens in many clinical settings. We sought to investigate all cases of rhabdomyolysis admitted to an acute hospital in Ireland over one calendar year. All cases of rhabdomyolysis admitted to a tertiary hospital over a 12-month period were reviewed. It was defined as serum creatine kinase greater than five times upper limit normal. The incidence, presenting characteristics and clinical outcomes, was collected from electronic records, electronic consult system and discharge summaries. Rhabdomyolysis was observed in 306 (1.7%) of all 18,297 admissions. It was seen most commonly in the setting of acute coronary syndrome (19.6%), post-operative state (18.0%), long-term confinement in the same position (16.3%), infection (9.2%) and seizures (6.5%). Overall mortality in this group was 16%. Acute kidney injury occurred in 43% of patients. Those with severe acute kidney injury (stage 3) had a mortality of 50%. Length of stay was significantly prolonged in the presence of acute kidney injury ($p < 0.001$). Surprisingly, in 44% of those with acute kidney injury, nephrology advice was not requested. Rhabdomyolysis is a common and a serious clinical condition across many specialties in an acute hospital that would likely benefit from nephrology involvement should acute kidney injury supervene.

Keywords Acute kidney injury · Rhabdomyolysis

Introduction

Rhabdomyolysis is a state of skeletal muscle necrosis with resultant leakage of intracellular contents such as myoglobin and creatine kinase (CK) into systemic circulation [1, 2]. It was first described in German medical literature in 1881. The hypothesis of myoglobin-related nephrotoxicity was later confirmed during review of crush injuries sustained in the Blitz in the Second World War in 1944 [3]. Aetiology is diverse including drugs, toxins, infections, muscle hypoxia, trauma, exertion, immobilisation, metabolic or electrolyte disorders. The clinical spectrum ranges from asymptomatic elevation in serum CK to life-threatening condition. The classical clinical triad of myalgia, pigmenturia and muscle weakness is present in less than 10% of patients [1]. Symptoms may be nonspecific or absent in up to 50% of patients [2]. The gold standard for diagnosis is elevation of serum CK but there is no consensus on the threshold for diagnosis [1]. It may be complicated by acute kidney injury (AKI), compartment syndrome or disseminated intravascular coagulation [1, 2, 4]. AKI is multifactorial being attributed to vasoconstriction, hypovolaemia, ischaemia, renal tubular obstruction and myoglobin-induced oxidative direct tubular toxicity [2]. Mortality from rhabdomyolysis is 10%; this is increased in the setting of AKI [2]. There are no reports in the Irish literature about rhabdomyolysis in an acute hospital setting. We sought to evaluate all cases of rhabdomyolysis admitted to hospital during one calendar year assessing the causes, severity, management and outcome, and, in particular, the role of our nephrology service.

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Methods

All cases of rhabdomyolysis admitted to a tertiary hospital over a 12-month period were reviewed. Ethical approval was granted by the Institutional Review Board. Rhabdomyolysis was defined as elevation of serum CK greater than five times upper limit normal. Inclusion criteria consisted of patients aged

greater than 18 years admitted to tertiary hospital within the defined 12-month timeframe. A total of 1093 samples of serum CK greater than five times upper limit normal were identified on electronic laboratory records; of these, 306 cases met the inclusion criteria. Data was collected retrospectively from the electronic medical records, discharge summaries and electronic consult system including: gender, age, patient location, baseline serum creatinine, peak serum creatinine, peak CK, length of stay, mortality, aetiology, presence of AKI, AKIN staging, need for dialysis and whether nephrology consult was requested. For statistical analysis, CK was censored at > 20,000 IU/L. Results are presented as number and percent, as mean and standard deviation, or as median and interquartile range. Differences in means were tested using independent *t* test. Linear regression analysis was used to explore the association between length of stay and AKI both before and after adjusting for potential confounding variables (age, gender, aetiology, peak CK level, baseline creatinine level). Statistical analysis was performed using IBM SPSS for Windows version 21.0 (Armonk, NY).

Results

There were a total of 18,297 adult admissions in the period studied: 6907 (37.7%) surgical and 11,390 (62.3%) medical. Rhabdomyolysis occurred in 306 (1.7%) of all admissions: 91 (1.3%) surgical and 217 (1.9%) medical. Given the estimated population size of our catchment area at 450,000 and excluding patients from outside catchment ($n = 39$), the estimated incidence was 0.59/1000 of the population. The prevalence of rhabdomyolysis amongst surgical specialties was further subdivided: vascular 10/353 (2.8%), urology 7/1104 (0.6%), upper gastrointestinal 18/828 (2.2%), orthopaedic 33/2367 (1.4%), otorhinolaryngology 1/283 (0.3%) and colorectal 22/1653 (1.3%). This was not applicable to medical admissions because patients were admitted under acute unselected general take rather than under the care of specialist services.

We reviewed all 306 cases identified. The mean (standard deviation) for age was 58(19) years; 68% were male, 32% were female. Median (interquartile range) for CK was 1726 (1157–1725) IU/L. Median (interquartile range) length of stay was 10 (5–25) days. Total mortality was 16%. Rhabdomyolysis was seen most commonly in the following settings: acute coronary syndrome (19.6%), post-operative (18.0%), long-term confinement in the same position (16.3%), infection (9.2%), seizures (6.5%), trauma (5.6%) and drugs and toxins (5.2%). A secondary contributory factor was noted in 111/306 (36%) of cases, the majority 51/111 (46%) being infection. Urine myoglobin was tested in 102/306 (33%) of cases. It was negative in 78/102 (76%) and positive in 24/102 (24%). The nephrology service was involved in 22% of cases; a nephrology consultation was requested in 14% of cases and 8% were under the care of nephrology.

AKI was present in 43% (130/306) of cases. Of those with AKI, the AKIN stages were as follows: AKIN 1 in 38% (49/130), AKIN 2 in 21% (27/130), AKIN 3 in 41% (54/130). Of those with AKI, 56% (73/130) neither had a nephrology consult nor were under care of nephrology. Median (interquartile range) for length of stay was more than twice as long in the presence of AKI at 17 (8–42) days compared to 8 (5–16) days in those without AKI ($t = 4.52$, $p < 0.001$). In the linear regression model, AKI was associated with length of stay, both unadjusted ($r^2 = 0.073$, $p < 0.001$) and after adjustment for confounding variables including age, gender, aetiology, peak CK level and baseline creatinine level (adjusted $r^2 = 0.102$, $p < 0.001$).

We further analysed the AKIN 3 subgroup (Table 1). The median (interquartile range) peak CK was 2782(1282–7382) IU/L. The majority (91%) was managed in a high dependency unit or intensive care unit setting with a high mortality at 27 of 54 (50%). Median (interquartile range) length of stay was 13(6–29) days. Nephrology consult was requested in 54% (29/54) of cases, whilst 28% (15/54) were already under the care of nephrology. Acute dialysis was needed in 59% (32/54). The need for acute dialysis was most commonly seen in the following settings: infection (28.1%), cardiac arrest (18.8%), post-operative state (15.6%), long-term confinement in the same position (6.3%), drug and toxins (6.3%), trauma (3.1%). A secondary contributory factor was noted in 16/32 (50%) with the principal factor being infection in 9/16 (56%).

Discussion

In a survey of all cases admitted to a tertiary hospital, rhabdomyolysis was noted in 1.7%, giving an estimated incidence in the catchment area of 0.59/1000 of the population. The causes were multifactorial being diagnosed in both acute surgical and acute medical cases. There was a high prevalence of AKI at 43%. International surveys have found a variable incidence of rhabdomyolysis-induced AKI ranging from 13 to 50% [1, 5]. The presence of AKI is associated with worse prognosis [2, 5].

Table 1 Characteristics of AKIN Stage 3 ($N = 54$)

Peak CK, IU/L*	2782 (1282–7382)
Length of stay, days*	13 (6–29)
Nephrology consult, *n* (%)	29 (54)
Under care of nephrology, *n* (%)	15 (28)
In HDU/ICU, *n* (%)	49 (91)
Acute dialysis, *n* (%)	32 (59)
Mortality, *n* (%)	27 (50)

*Results given as median (interquartile range)

One study described a mortality rate of 8% in those without AKI and 42% in those with AKI [6]. This was reflected in our survey; we noted 50% mortality in AKIN 3 subgroup. International mortality data is widely variable being dependent on study population, principal aetiology and clinical setting [5]. For example, in a cohort of ICU patients, there was 59% mortality in those with rhabdomyolysis-induced kidney injury [7]. Conversely, in a study of 475 hospitalised patients whereby substance abuse was identified as principal aetiology; there was a mortality of 3.4% in those with rhabdomyolysis-induced kidney injury [8].

In clinical practice, CK remains the most sensitive biological marker to evaluate muscle injury, but there is no consensus on the threshold for diagnosis for rhabdomyolysis, varying from five- to tenfold the upper limit normal [1, 2]. In addition, there is no defined threshold of CK above which there is increased risk of rhabdomyolysis-induced AKI [5]. A recent meta-analysis suggested that the aetiology of rhabdomyolysis is an important aspect to consider when interpreting the predictive performance of CK. For instance, in trauma cases, there is a strong correlation between mean CK level and risk of AKI [9].

Although toxic accumulation of myoglobin is understood to be a factor in the pathogenesis of AKI, testing for myoglobinuria has limitations. In a study of 87 cases, where rhabdomyolysis was defined as serum CK > 500 IU/L, urinary myoglobin was negative in 26% [10]. In our study, urinary myoglobin was tested in one third of cases; of those, 76% were negative. False negatives are attributed to short half-life of myoglobin (2–3 h) [1, 4]. In addition, the renal threshold for myoglobinuria is not always met [5]. Serum myoglobin must exceed glomerular reabsorption capacity in order for it to be excreted in the urine [5]. Serum myoglobin has rapid unpredictable metabolism [5]. For these reasons, serum myoglobin has been disregarded for diagnostic purposes. However, a retrospective review of 484 patients with elevated serum myoglobin argues that it may have a role to play as an early predictor marker of rhabdomyolysis and myoglobin-related AKI [11].

The presence of rhabdomyolysis has implications for the cost of clinical care. A retrospective population-based cohort study of 555,043 patients who underwent urology oncology surgery over a 10-year period demonstrated that whilst post-operative rhabdomyolysis was an uncommon complication (0.001%), it was associated with length of stay being twice as long (incidence risk ratio = 1.83, 95% CI 1.56–2.15, $p < 0.001$) with an adjusted 90-day median hospital direct costs USD 7515 higher than those without post-operative rhabdomyolysis ($p < 0.001$) [12]. In our survey, the principal determinant of length of stay in patients with rhabdomyolysis was AKI. A surprising finding of our study was the lower than expected role of nephrology service in the care of patients with rhabdomyolysis; 56% of patients with rhabdomyolysis-induced AKI were not linked to the nephrology service. Nephrology consultation could not only have a role in improving patient outcome but could reduce the cost of care.

Our survey had a few limitations. Firstly, in the absence of formal diagnostic criteria, it is difficult to evaluate the true prevalence of rhabdomyolysis and rhabdomyolysis-induced AKI. Not all patients with elevated CK levels were included because we set our threshold for CK at five times upper limit normal. Milder cases of rhabdomyolysis may have been excluded. Secondly, not all admissions had CK levels tested; so, it is possible that not all cases of rhabdomyolysis were identified. Given the findings about the significant relationship between LOS and AKI, a further study would be needed in order to validate this conclusion.

In conclusion, rhabdomyolysis is not an uncommon problem in an acute hospital setting with multiple aetiologies covering many hospital specialties. Rhabdomyolysis-induced AKI has substantial implications for morbidity, mortality and cost of care. Early recognition and specialist management are key to better outcomes in rhabdomyolysis.

Compliance with ethical standards

Ethical approval was granted by the Institutional Review Board.

Conflicts of interest The authors declare that they have no conflict of interest.

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