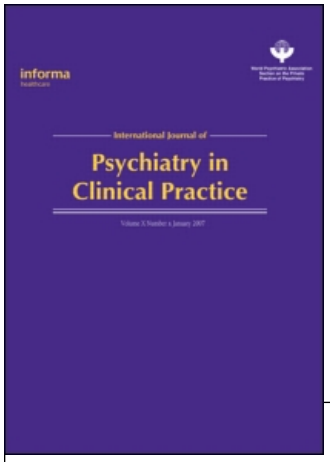

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Elevated serum creatine kinase levels in psychiatric practice: differential diagnosis and clinical significance: A brief, practical guideline for clinicians

Viktor Voros [a]; Peter Osvath [a]; Sandor Fekete [a]; Tamas Tenyi [a]
[a] Department of Psychiatry and Psychotherapy, University of Pecs, Pecs, Hungary

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ORIGINAL ARTICLE

Elevated serum creatine kinase levels in psychiatric practice: differential diagnosis and clinical significance: A brief, practical guideline for clinicians

VIKTOR VOROS, PETER OSVATH, SANDOR FEKETE & TAMAS TENYI

Department of Psychiatry and Psychotherapy, University of Pecs, Pecs, Hungary

Abstract

Introduction. Elevated serum CK levels often occur in psychiatric in-patient practice. Although the majority of cases are benign and temporary, it is important to recognize and treat these conditions. *Aims.* To discuss the etiology, the clinical significance and the management of elevated creatine kinase levels in psychiatric in-patient practice, focusing on antipsychotic-induced rhabdomyolysis. To compare the pathogenesis and the clinical features of rhabdomyolysis and neuroleptic malignant syndrome. *Methods.* Review of the literature. *Results.* A brief, practical guideline is introduced, which may help clinicians in the differential diagnosis and in the management of patients with elevated creatine kinase activity in emergent psychiatric practice. *Conclusions.* The most common etiologic factors (prescription drugs, alcohol, physical reasons, cardiac etiology) and clinical syndromes (rhabdomyolysis, neuroleptic malignant syndrome, acute coronary syndrome) should be considered, when elevated creatine kinase levels are encountered in psychiatric in-patients. Routine creatine kinase measurements in asymptomatic patients on antipsychotic medications are not recommended, but patients should be carefully followed for the development of rhabdomyolysis, when muscular symptoms arise. Careful monitoring of symptoms and potential complications is critical in order to avoid devastating clinical consequences. Cautiously challenging patients with another antipsychotic after an antipsychotic-induced rhabdomyolysis is recommended to decrease the possibility of recurrence.

Key Words: *Creatine kinase, rhabdomyolysis, neuroleptic malignant syndrome, antipsychotics, guideline*

Introduction

We discuss the clinical significance of elevated serum creatine kinase (CK) levels in psychiatric in-patient practice, focusing on antipsychotic (AP)-induced rhabdomyolysis (RML). Although the majority of cases are benign and temporary, CK elevation may represent a severe, life-threatening syndrome, such as neuroleptic malignant syndrome (NMS). In other cases, the accumulation of CK in the blood can lead to clinical complications, such as acute renal failure (ARF). The most common factors resulting in CK level elevations in psychiatric in-patients are shown in Table I. Besides physical reasons, the most common causes of CK elevations are alcohol abuse and drug-induced RML caused by psychotropic medications.

Methods

We reviewed relevant cases from our institution and identified the most common features associated with CK level elevations. In addition, we reviewed the English language literature by performing a detailed Medline search between 1996 and 2006 with the following keywords: creatine kinase, rhabdomyolysis, antipsychotics. We found a total of 22 articles; further review showed that seven were relevant to our topic. These papers were carefully reviewed and were included in this analysis. Relevant case reports were also included.

Results

RML is a common, potentially lethal clinical syndrome resulting from acute myocyte necrosis with leakage of muscle constituents into the circulation. Myoglobinuria (MGU) is the most significant consequence leading to ARF in 15–33% of patients with RML [1]. Physical exercise and exogenous toxins such as illicit drugs, alcohol and prescription drugs have been reported as the most common causes. Among prescription drugs, APs, cholesterol-lowering agents, zidovudine, colchicine, selective

Correspondence: Viktor Voros, MD, H-7623 Pecs, Ret u. 2, Hungary. Tel: +36 72 535900. Fax: +36-72-535951. Email: viktor.voros@aok.pte.hu

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Table I. The most common reasons of serum creatine kinase level elevations in patients treated on psychiatric wards.

- Typical causes for elevated CK level (with normal CK-MB fraction)
  - Intramuscular injections
  - Physical restraint (violent and assaultive behavior)
  - Physical trauma (fall, fight, restraint)
  - Extreme physical activity (mania, delirium, psychomotor agitation)
  - Seizure (alcohol or benzodiazepine withdrawal, epilepsy)
  - Toxic (alcohol, illicit drugs)
  - Drug-induced
    - Psychotropic drugs: antipsychotics, antidepressives, lithium
    - Non-psychotropic drugs: cholesterol-lowering agents, β-blockers
- Some other possible reasons for CK level elevation
  - Cardiac disorders (elevated CK-MB): acute coronary syndromes, myocarditis
  - Central nervous system disorders (elevated CK-BB): stroke, intracerebral hemorrhage, meningitis, encephalitis, epilepsy
  - Muscular disorders: muscle fiber damage (muscle trauma, hematoma), polymyositis, dermatomyositis, muscular dystrophy, McLeod myopathy, Marinesco-Sjögren syndrome, rhabdomyolysis
  - Thermal exposure: freezing, burns
  - Gastroenterological disorders: necrotizing pancreatitis, acute hepatic necrosis
  - Malignant neoplastic disorders
  - Endocrinological disorders: thyrotoxicosis, hypoparathyreosis, hypoadrenalism
  - Metabolic reasons: electrolite imbalance, rapid correction of hyponatremia
  - Infectious disorders: Coxsackie-B virus, trichinosis
  - Vascular disorders: arterial occlusion, embolization
  - Others: postoperative states, sepsis, pregnancy, resuscitation

serotonin reuptake inhibitors (SSRIs) and lithium have been most frequently implicated [1].

In alcohol-related RML reported in the literature, most patients have a typical history of short-term alcohol intoxication with sedation, immobilization or alcohol-induced coma [2]. These circumstances lead to muscle compression and muscular ischemia, which will accelerate short-term alcohol myotoxicity. In long-term alcohol abuse, RML develops because of electrolyte abnormalities, nutritional deprivation or peripheral neuropathy [2].

Meltzer reported more than 30 years ago on increased serum CK activity in some hospitalized acutely disturbed patients with schizophrenia [3]. Some of these increases did not result from non-specific factors such as activity or trauma. Those patients who showed increased CK activity had more florid psychopathology and tended to have higher CK levels in non-acute periods than those without increases. The author concluded that the investigation of CK might have considerable heuristic value for the study of schizophrenia and other psychoses [3].

A possible explanation for the pathogenesis of RML in patients treated with APs is increased muscle cell permeability, since APs may enhance the destruction of myocytes [4,5]. Furthermore, while first-generation antipsychotics (FGAs) predominantly develop their clinical effect through central dopaminergic blockade, second-generation antipsychotics (SGAs) also exert their effects by strongly blocking different serotonin (5-HT) receptors. It has been shown in rodents that 5-HT can be toxic to skeletal muscle [6] and that drugs with a relatively potent inhibitory effect on 5-HT_{2A} receptors can cause muscle damage and RML in some patients [7,8].

NMS, which develops in response to central dopaminergic blockade, has to be distinguished clinically from the peripheral, mainly benign syndrome of RML characterized by CK elevation and muscle symptoms (Table II). NMS is characterized by extreme CK elevation, hyperthermia, muscular

Table II. The comparison and the differential diagnosis of neuroleptic malignant syndrome and rhabdomyolysis.

	NMS	RML
Terminology	Neuroleptic malignant syndrome	Rhabdomyolysis
Etiology	Drug-induced (antipsychotics)	Drug-induced, others
Possible pathogenesis	Central dopaminergic blockade in the central nervous system	Peripheral serotoninergic blockade in the muscles
Clinical features		
Dominant symptom	Disturbance in consciousness	Muscle pain and fatigue
Autonomic system	Increased pulse, blood pressure	No significant disturbances
Creatine kinase level	Extremely elevated	Elevated (sometimes extremely)
Muscular symptoms	Rigidity, dystonia, tremor	Pain, fatigue
Body temperature	Hyperthermia, pyrexia	Low-grade fever
Consciousness	Confusion, coma	No disturbance in consciousness
Behavior	Obtundation, agitation	Prostration
Others	Incontinence, leukocytosis, mutism, diaphoresis, dysphagia	Flu like symptoms
Complications	Coma, death (10–30%)	Acute renal failure (15–33%)
Prognosis	Malignant	Benign
Treatment	Intensive care	Symptomatic (forced diuresis)

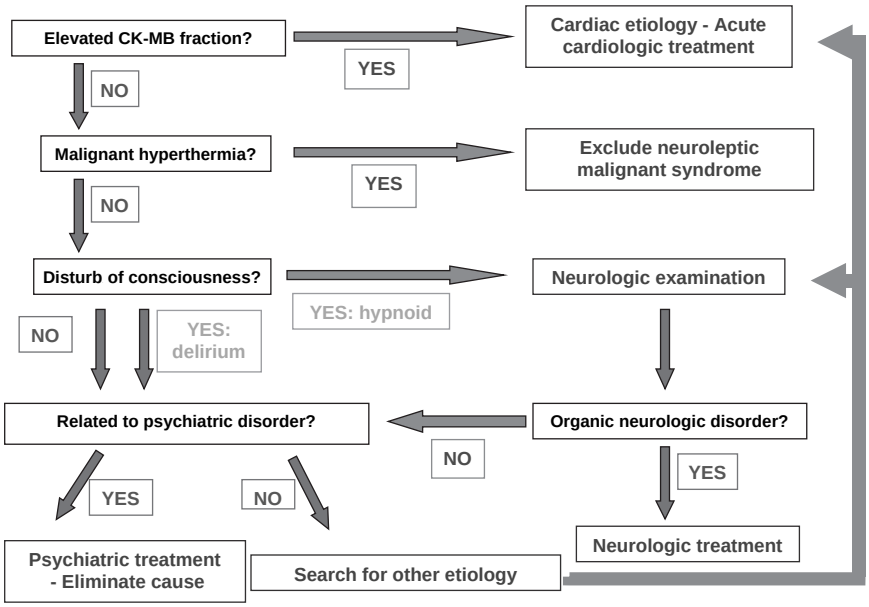

Figure 1. Clinical guideline to the differential diagnosis and management of acute serum creatine kinase level elevations in emergency psychiatric practice.

rigidity, disturbance of consciousness and often poor prognosis. On the other hand, RML consists of CK elevation (in some cases extreme), low-grade fever (but not hyperthermia or pyrexia), muscular symptoms (mild pain, fatigue, but not severe dystonia), no disturbance of consciousness and benign prognosis.

The management of elevated CK levels includes acute symptomatic therapy with abundant hydration and forced, high-volume alkaline diuresis (to keep urine output at 300 ml/h) or hemodialysis in more severe cases. Monitoring renal function using blood urea nitrogen (BUN), creatinine measurements, urine output and myoglobin are essential to guide management. Careful monitoring of vital signs such as temperature, heart rate, blood pressure and electrocardiographic monitoring are also critical.

Specific therapy depends on the results of the systematic examinations and the level of serum CK activity. Elevated CK levels should be defined based on reference ranges in individual local laboratories (e.g., CK $>$100 U/l). CK measurement has to be repeated after 48 h of rest, but sometimes it is difficult to carry out, especially in emergency psychiatric in-patients.

The guideline outlined in Figure 1 may aid clinicians in the differential diagnosis and in the management of patients with acute serum CK level elevation in emergency psychiatric practice.

Discussion

The most common etiological factors (prescription drugs, alcohol, physical reasons, cardiac etiology) and clinical syndromes (acute coronary syndrome / ACS/, RML, NMS) should be considered when elevated CK levels are encountered in psychiatric in-patients [9] (Figure 1).

Extreme elevations in CK should be managed immediately by forced diuresis to prevent further possible clinical complications. Since CK elevations or even frank RML can be recurrent, discontinuation of the culprit drug is mandatory. Routine CK measurements in asymptomatic patients on antipsychotic medications are not recommended, but patients should be carefully followed for the development of RML, when muscular symptoms arise. It is critical to check serum CK levels when patients complain about any muscular symptoms (fatigue, pain, rigidity). We also suggest cautiously challenging patients with another AP after an AP-induced RML to decrease the possibility of recurrence [10]. Careful monitoring of symptoms and potential complications is critical in order to avoid devastating clinical consequences.

Key points

- The most common etiological factors and clinical syndromes should be considered, when elevated creatine kinase levels are encountered in psychiatric in-patients
- Drug-induced rhabdomyolysis is mainly caused by psychotropic medications, such as antipsychotics
- Routine creatine kinase measurements in asymptomatic patients on antipsychotic medications are not recommended, but patients should be carefully followed for the development of rhabdomyolysis, when muscular symptoms arise

- Cautiously challenging patients with another antipsychotic after an antipsychotic-induced rhabdomyolysis is recommended to decrease the possibility of recurrence

Statement of interest

None of the authors have any conflicts of interest to disclose.

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