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The Journal of Critical Care Medicine 2020;6(4):249-252

CASE REPORT

DOI: 10.2478/jccm-2020-0032

Rhabdomyolysis-Induced Acute Renal Injury in a Schizophrenic Patient

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Abstract

Nowadays, schizophrenia is treated with atypical antipsychotics that can determine neuroleptic malignant syndrome or rhabdomyolysis appearance. In addition to trauma and muscular hypoxia, there are some drugs and toxins associated with rhabdomyolysis development, among which olanzapine. A case of severe rhabdomyolysis syndrome, with extremely high levels of serum creatine kinase (CK), followed by acute kidney failure, secondary to olanzapine overdose and prolonged immobilization is outlined. Continuous renal replacement therapy was performed, with a slow clearance of serum CK levels. Under supportive therapy, systemic alkalinisation with volume resuscitation and corticotherapy, patient's general condition was improved, as well as his lower limb paresis. He followed frequent psychiatric evaluations and psychotherapies, before and after being transferred to a medical service. Rhabdomyolysis diagnosis is difficult in mild cases due to non-specific signs and symptoms, but it also has some typical manifestation, generically called "the rhabdomyolysis syndrome triad". The treatment is usually supportive; renal replacement therapy is required in the presence of acute kidney injury unresponsive to aggressive volume resuscitation. The systemic myoglobin release is responsible for renal injury. Olanzapine muscle toxicity can lead to severe rhabdomyolysis syndrome complicated with acute kidney injury and multiple organ dysfunction syndrome. Rapid identification and aggressive therapeutic management are essential for improving patients' outcome and prevent the occurrence of irreversible injuries.

Keywords: rhabdomyolysis, acute renal injury, olanzapine, prolonged immobilization, schizophrenia

Received: 16 June 2020 / Accepted: 7 September 2020

Background

Schizophrenia, a significant psychiatric disorder, is usually treated with atypical antipsychotics, among which olanzapine. The use of these substances is favoured compared with the typical agents due to the lower risk of extrapyramidal adverse events [1]. However, olanzapine is associated with significant side effects, especially weight gain, somnolence or mild fever and studies showed an increasing number of cases of neuroleptic malignant syndrome (NMS), severe rhabdomyolysis and acute kidney injury [2, 3].

Rhabdomyolysis, the destruction of striated muscle fibres and leakage of intracellular content into the systemic circulation, can be a life-threatening syndrome [4]. It is caused principally by trauma and exertion, but also by infectious agents or toxins, medications, various diseases (especially body-temperature extreme changes), electrolyte abnormalities, muscle enzyme deficiencies (genetic defects) and endocrinopathies [5, 6]. There are also some reported cases of idiopathic rhabdomyolysis, sometimes recurrent [7, 8]. Epidemiological reports show that non-traumatic causes are about five times more frequent [9, 10]. It can present itself as an asymptomatic increase in serum creatine kinase (CK) levels, or it can manifest through intensively high CK levels, subsequent myoglobinuria, hyperkalaemia and acute renal injury [11].

A case is described of severe rhabdomyolysis syndrome, with high levels of serum CK, followed by acute kidney failure, secondary to olanzapine overdose and prolonged immobilization.

Case Presentation

A 32-year-old man, under treatment by his general practitioner for schizophrenia and type III obesity, was referred to the Emergency Clinical Hospital, Bucharest,

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Romania, due to multiple organ dysfunction syndrome (MODS) secondary to severe rhabdomyolysis. At the time of referral, he was being treated with 20 mg oral olanzapine (Olanzapină Actavis©, Actavis Group PTC, Hafnarfjörður, Islanda) once daily.

On admission to the hospital, he was conscious, sleepy, temporal and spatial disoriented, presenting with lower limb paresis, without no signs of compartment syndrome, and a temperature of 38.5°C.

In the emergency department (ED), a series of examinations were performed, which suggested a diagnosis of multiple organ dysfunction syndrome (MODS). The laboratory results showed CK levels > 160.000 U/L (reference range 30-135 U/L), creatine kinase myocardial band level (CK-MB) 15.000 U/L (reference range 10-16 U/L), severe leucocytosis 27.89 x 10^3/µL, haemoconcentration (haemoglobin 18.65 g/dL), serum creatinine 5.70 mg/dL (normal range 0.70-1.40 mg/dL), blood urea 87 mg/dL (normal range 19-43 mg/dL), serum aminotransferase (AST (TGO) 3421 U/L – normal range 14-50 U/L, ALT (TGP) 530 U/L – normal range 10-50 U/L), mild hyponatremia and severe hyperkalaemia (potassium 6.72 mmol/L). The computed tomography examination revealed no acute pathological modification. After 3 hours in the ED the patient remained anuric.

In the presence of severe rhabdomyolysis, with subsequent MODS, the patient was admitted directly into the Intensive Care Unit. Based on above laboratory findings and persistent anuria, the diagnostic of acute kidney injury (AKI) was established (AKIN Classification: Stage 3), and continuous veno-venous haemodiafiltration was started in order to prevent further kidney damage and to clear the serum creatine kinase, additionally using a CytoSorb® cartridge.

A toxicologist had evaluated the patient, in the first hours after ICU admission, and according to DMS-5 diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders), NMS was excluded.

From the time of admission and continuing over the following days, the patient received systemic alkalinization with volume resuscitation and short-term high corticosteroids doses.

According to the hospital's protocol, at admission, full bacteriologic and viral screening were performed, and despite persistent hyperthermia, which had persisted for three days after ICU hospitalization, all the results were negative.

The variation over time of different laboratory findings is presented in Figure 1 and Figure 2.

Continuous renal replacement therapy (CRRT) was performed for six days, with frequent changes of the dialysis filter in the first 72 hours, to ensure optimum mediator reduction in the face of this extremely severe rhabdomyolysis.

After six days, the serum CK values gradually decreased, the renal function progressively improved with a progressive resumption of diuresis, continuous veno-venous haemodiafiltration was stopped. Intermittent haemodialysis therapy was initiated, in the dialysis department, for another week (four sessions), until creatinine and blood urea levels remained within the normal range (serum creatinine 1.37 mg/dL and urea 39 mg/dL), with a spontaneous urinary flow of around 1mL/kg/hr.

After a few sessions of psychotherapy, started in the sixth day after ICU admission, and frequent psychiatric evaluations, the patient, revealed the fact that he consumed 15 tablets of olanzapine in the last 48 hours

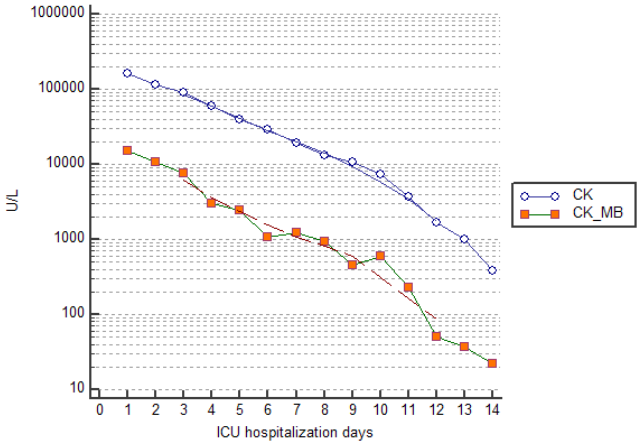

Fig. 1. Evolution of CK and CK-MB levels

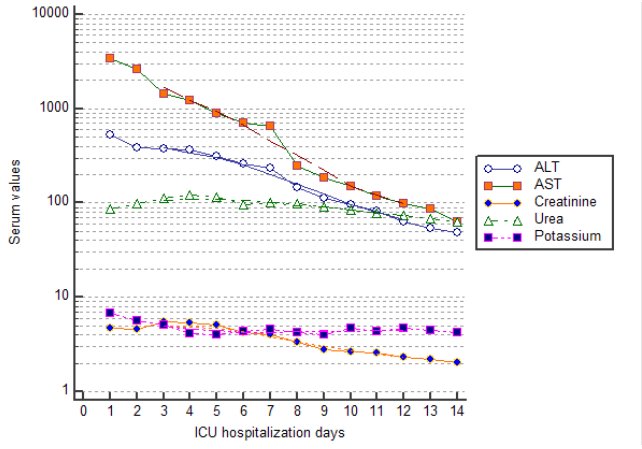

Fig. 2. Variations of different laboratory findings

before hospital admission. During that period he admitted to losing consciousness and probably compressing his lower limbs under his body weight.

Although on admission to the ICU he presented lower limb paresis, there was no motor deficit after a few days, and the patient started physical therapy.

The evolution was favourable with a gradual remission of the clinical picture of MODS. After two weeks of hospitalization in the ICU, he was transferred to the internal medicine department, where he was kept under psychiatric surveillance. He was discharged home after another three days.

The particularity of this case is that, in the absence of NMS and rigidity, it remains unclear if the cause of the extremely severe rhabdomyolysis was the prolonged immobilization, the olanzapine overdose and its toxicity or both.

Discussion

This case shows the development of rhabdomyolysis in the absence of NMS, rigidity or tremor, with extremely high levels of CK. Like other reported cases, olanzapine seems to be the causative agent, by direct muscular toxicity, as there was no evidence of infection, myocardial infarct or important dyselectrolytemia, but only paresis, persistent muscle weakness and hypotonia [2].

Severe rhabdomyolysis syndrome is frequently associated with electrolyte imbalance, acute renal failure and cardiac arrhythmia. There are reported cases complicated with disseminated intravascular coagulation (CID) [5, 10]. Diagnosis is difficult in mild cases due to non-specific signs and symptoms. However, it has also some typical manifestations, which were present as well in our case, like muscle weakness, myalgia and urinary hyperpigmentation, so-called by some authors "the rhabdomyolysis syndrome triad" [4, 12].

The treatment for rhabdomyolysis syndrome is usually supportive of allowing the patient a safe return to baseline levels, without invasive manoeuvres. Nevertheless, in severe cases, as it was the case of our patient, renal replacement therapy is required in order to save a patient's life and to prevent extensive damage to renal function. It is of greater importance in patients with chronic kidney disease or concomitant cardiovascular diseases for improving the outcome [13, 14]. There are three different mechanisms responsible for renal injury, secondary to myoglobin release: severe renal vasoconstriction, intratubular casts formation and direct toxicity on the renal tubular cells [15, 16].

Therefore, AKI is one of the most severe complications of this syndrome, appearing secondary to myosin accumulation in the renal tubular system with subsequent necrosis. When CK levels overcome 15.000 U/L, the rate of AKI development is greater than 70% [17]. The mortality rate associated with rhabdomyolysis is 8-10% in mild cases, exceeding 42% of AKI develops [18], prompt and proper therapeutic management being the key to success.

Other severe complications of rhabdomyolysis syndrome, also present in our case, are acute liver failure and MODS. Acute liver failure, probably due to drug-induced cytolysis, appears because of liver inflammation, secondary to liver protease leakage. It has an overall incidence of 25% in patients with olanzapine-induced rhabdomyolysis [17]. MODS, the leading cause of death in severe rhabdomyolysis, results secondary to a massive release of cytokines and inflammatory mediators into the systemic circulation [19]. Early prompt and proper treatment with aggressive volume resuscitation, systemic alkalinization, haemodialysis in the face of AKI, correction of electrolyte imbalance and corticosteroids can improve patients' outcome and limit the long-term disabilities [20-22].

Waring et *al.* published a study about the olanzapine overdose and subsequent acute muscle toxicity, and they discovered that > 17% of patients presenting for olanzapine ingestion had developed dose-dependent muscle toxicity, with increased levels of CK. Like in our case, a significant limitation is due to the impossibility of determining serum olanzapine concentration [23]. More studies pointed out the fact that CK values elevation appears after 12-hours post ingestion [2, 14, 17]. Therefore, repeated laboratory determinations are required for proper management.

Conclusion

Olanzapine muscle toxicity can lead to severe rhabdomyolysis syndrome complicated with AKI and MODS. Rapid identification, periodic monitoring of CK levels changes and aggressive therapeutic management are essential for improving patients' outcome and prevent the occurrence of irreversible injuries. When AKI develops, renal replacement is frequently required even in the presence of rapid and prompt volume resuscitation and systemic alkalinization.

Acknowledgement

The authors declare no conflict of interest regarding this article. All the procedures of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed written consent was obtained.

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