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REVIEW ARTICLE

Rhabdomiolysisin the Elderly

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ABSTRACT

Rhabdomyolysis is a common clinical syndrome characterized by triad of symptoms that include muscle pain, weakness and dark urine. More than 50% of the patients do not complain of muscle pain or weakness and the classic triad is seen in<10% patients. In the USA 25.000 cases are reported annually, and in 7% of all cases is reported Acute Kidney Injury (AKI). The diagnosis is describe on the elevation of creatine kinase >10 times the normal value. The objective in management is to prevent or treat AKI and complications rhabdomyolysis-related in adult and in the elderly patients.

Introduction

Rhabdomyolysis results from the rapid breakdown of skeletal muscle fibers, that it ranges from an asymptomatic illness with elevation of Creatine Kinase (CK) level associated with electrolyte imbalances, acute renal failure and disseminated intravascular coagulation [1-3]. The symptomatology includes muscle pain, weakness and dark urine observed in <10% patients. More than 50% of the patients do not complain of muscle pain or weakness [3-4]. The most sensitive marker of myocyte injury is Total CK level. A 5-fold elevation of CK is considered as diagnostic of rhabdomyolysis by majority of authors [5-6]. The concentration of CK is directly proportional to the extent of muscle injury [7] and it is a predictor of developing of Acute Renal Failure (ARF) [8].

Epidemiology

In the USA more than 25.000 cases are reported annually. About 7% of all cases of rhabdomyolisys had acute kidney injury (AKI) [9]. AKI from rhabdomyolysis is common in ~5% of the children than the risk reported for adults and the elderly [10]. It has been reported that there are close to 200 medications and toxins known to cause skeletal muscle injury [11-13]. Rhabdomyolysis can be induced by methadone abuse [14,15] and it may be a complication of acute viral infection (i.e. influenza, coxsackie and herpes viruses)[16]. In addition, have been reported also some cases of rhabdomyolysis associated with Cytomegalovirus (CMV) infection [17-18].

Diagnostic Tests Used in the Evaluation of Rhabdomyolysis

Diagnosis is based on the elevation of creatine kinase >10 times the normal value. It increases within 2–12 hours of muscle injury, peaks around 24–72 hours, and then reduces over the next 3–5 days (Figure 1) [18-20]. Other

complications, including hyperkalemia, hyperphosphatemia, hypocalcemia, lactic acidosis, compartment syndrome and disseminated intravascular coagulation can occur in rhabdomyolysis [21-23]. If the cause is suspected to be a drug, it should be discontinued promptly [9]. Renal function and electrolytes should be monitored closely. Diagnostic tests used in the evaluation of rhabdomyolysis are reported in Table 1. Other reports showed that pheochromocytoma could induce rhabdomyolysis and AKI with increased creatine kinase levels [24-26].

Statin-Associated Myopathies (SAM)

Rhabdomyolysis has been reported as a major statin-associated adverse effect. The highest rate of SAM has been reported for simvastatin [27]. The incidence of rhabdomyolysis is of ~0.1% [28] and the development of SAM is dose-dependent [29]. Severe cases of SAM have been reported in patients under dosed and without interfering medication. Concomitant treatment of colchicine and simvastatin may exacerbate its myotoxic effect [30]. Different study has been reported that advanced age, female sex, presence of comorbidities, and alcohol consumption are further predisposing factors for SAM. Concomitant therapy should be checked for potential interaction with statins, including herbal cures. Clinical monitoring of SAM may include baseline CK levels of patients, renal function, electrolyte disorders, genetic myopathy in the past medical history, or significant alcohol abuse [31].

What is in the elderly?

There is still no definitive indication of statin therapy in the low-risk elderly due to a lack of evidence from clinical studies or meta-analyses (cited in Class IIb and Level of evidence in European Society of Cardiology guidelines) [32].The 2013 American College of Cardiology and American Heart Association Blood Cholesterol Practice Guidelines recommend the use of moderate-intensity statins in patientsolderthan75years to prevent myopathy. However, in clinical practice, aggressive statin therapy is often prescribed for significant coronary disease. Prescribing high-intensity statins for patients with advanced age, such as this case, may increase the risk of rhabdomyolysis and other complications [33]. It has been reported that in aged 65–78 years treated with atorvastatin with a maximum dose of 80 mg daily and followed for a median period of 53.9 months weren't documented cases of rhabdomyolysis or myopathy. This ALLIANCE study demonstrates that older patients experience no benefit or safety issues with an aggressive atorvastatin regimen [34].In other studies, it has been reported that the risk of myopathy is higher in patients aged over 80 years. In fact, this issue is crucial in older patients with poly-pharmacy, presence of comorbidities, reduced muscle mass impaired renal and liver function [35]. Although, in older patients, statins remain underused and only about half of those who should benefit were treated, it has been reported, that patients with age >65 years are less likely to receive a statin prescription compared with their younger patients [36-38]. In conclusion, statins seems to be relatively safe in the older population, in terms of muscle adverse effects.SAM seems to be relatively safe in the older population, in terms of muscle adverse effects. Future study may be crucial for evaluation the lights and the shadows in the treatment of elderly patients with statins.

Figure 1: CK rises within 2–12 hours of muscle injury, peaks around 24–72 hours, and then declines over the next 3–5 days, from Ciarambino et al. [18].

Table 1: Diagnostic tests used in the evaluation of rhabdomyolysis.

• History
• Assess the level of consciousness
• Check for signs of: Dehydration, Systemic infection, Trauma, Compartment syndrome and Exertion heat stroke
• Check medication use:Antipsychotics (haloperidol, fluphenazine, perphenazine, chlorpromazine), Cyclic antidepressants and selective serotonin reuptake inhibitors, Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, cerivastatin), Fibric acid derivatives (bezafibrate, clofibrate, fenofibrate, gemfibrozil), Quinine, Salicylates, Theophylline, Antibiotics (fluoroquinolones, pyrazinamide, trimethoprim/sulphonamide, amphotericin B, itraconazole, levofloxacin), Zidovudine, Antihistamines, Aminocaproic acid, Phenylpropanolamine, Sodium valproate, Anaesthesia with volatile anaesthetics a/o succinylcholine, Benzodiazepines, Corticosteroids
• Vital signs: Check for signs of hypovolaemia and shock
• Serum CK: Elevated as a result of muscular damage: >5, >10, >20 or even >50 times the upper limit normal
• Serum potassium: Elevated levels indicate muscular damage and potassium leakage from cells
• Serum sodium: Check for exercise-associated hyponatraemia
• Renal function: Blood urea nitrogen and serum creatinine—assess renal function and hydration status.An elevated ratio may suggest dehydration, and an elevated creatinine level may suggest renal dysfunction
• Myoglobinuria: Presence of urine myoglobin suggests muscular damage.Absence of urine myoglobin does not preclude exertionalrhabdomy lisis
• Acid base status: Check for metabolic acidosis
• Coagulation tests: Abnormal results may indicate disseminated intravascular coagulation
• ECG: Check for dysrhythmias if the patient has hyperkalaemia or other electrolyte abnormalities
• Cardiac isoenzymes: Rule out cardiac infarction
• Toxicology screening: Check blood and urine for (illicit) drug abuse

Complications

AKI has been reported in 10-20% of patients with rhabdomyolysis, and up to 5-9% of all AKI cases are caused by rhabdomyolysis [39]. Hypocalcemia is an important complication of rhabdomyolysis for which several pathogenic factors, including AKI, have been proposed. In fact, AKI facilitated hypocalcemia by exacerbating the hyperphosphatemic effects of muscle damage [39].Changes in serum calcium in rhabdomyolysis-associated acute renal failure might also be explained by the deposition or removal of mineral into or from necrotic muscle with the parathyroid and vitamin D changes occurring secondarily [40].

Therapy

1. Hydration

It is crucial to prevent AKI via intravenous administration of NaCl0.9% [3].Fluid resuscitation is imperative to prevent AKI [9]. In elderly patients, or in those with pre-existent heart disease, intravenous fluid therapy must be personalized and carefully monitored due to the risk of fluid over load and pulmonary edema. The role of osmotic agents (i.e., mannitol) or loop Diuretics (i.e., furosemide) should hence be discouraged [41]. It has been reported that the use of mannitol and/or bicarbonate comes mostly from animal studies and is inconsistent and conflicting [42].Patient monitoring is pivotal (the mortality rate is as high as 8%), and should be focused on preventing the detrimental consequences, that often include renal disease and coagulopathy. In the pre-hospital setting, forced hydration with 1.5-2 L of saline solution should be started immediately, followed by 1.5-2 L/h. Following hospital admission, continuous hydration should be ensured, alternating the saline solution with a 5% glucose solution [10].

2. Urinary catheter

For all patients it is needed monitor hourly urinary output.The treatment with fluid replacement is aimed at achieving at least 300 ml /h of urine excretion.

3. Urine alkalization

It is crucial prevent AKI by urine alkalization with, via intravenous, sodium bicarbonate administration. It has been reported that sodium bicarbonate, prevent myoglob in precipitation into the renal tubuli, and may help managing of hyperkalemia associated or not with metabolic acidosis [43].

4. Hyperkalemia

Hyperkalemia must be managed using the usual techniques. It has been reported that treatment with glucose and insulin may be ineffective due to inability of damaged muscle tissues to capture potassium from the extracellular liquid.

5. Hypocalcemia

The administration of intravenous calcium (both chloride and gluconate) should be used only to treat life-threatening ECG alterations, secondary to hyperkalemia or extreme hypocalcemia [44-46]. Aggressive hydration might reduce the incidence of hypocalcemia in rhabdomyolysis [40].

6. Haemodialysis

Some patients with severe AKI may need hemodialysis. High volume haemofiltration or super high flux haemodialysis has been used for extracorporeal elimination of myoglobin in severe cases [42].

Conclusion

Rhabdomyolysis remains a relatively rare condition, but it clinical consequences are frequently dramatic in terms of both morbidity and mortality, in particular in older patients. The main objective in management is to prevent or treat AKI. In conclusion, SAM seems to be relatively safe in the older population, in terms of muscle adverse effects. Future study may be crucial for evaluation the lights and the shadows in the treatment of elderly patients with statins to prevent the adverse effects, as AKI and electrolyte disorders. Clearly, studies are required, both Randomized Controlled Trials (RCTs) and meta-analyses to provide evidence on drug safety of statin therapy prescribed in older adults for primary prevention of Cardiovascular Disease (CVD) and further to facilitate optimal prescribing and management approaches to minimize the side effects.

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