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Review

Non-traumatic rhabdomyolysis: Background, laboratory features, and acute clinical management

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ABSTRACT

Rhabdomyolysis is a relatively rare condition, but its clinical consequences are frequently dramatic in terms of both morbidity and mortality. Although no consensus has been reached so far about the precise definition of this condition, the term rhabdomyolysis describes a rapid breakdown of striated, or skeletal, muscle. It is hence characterized by the rupture and necrosis of muscle fibers, resulting in release of cell degradation products and intracellular elements within the bloodstream and extracellular space. Notably, the percentage of patients with rhabdomyolysis who develop acute kidney injury, the most dramatic consequence, varies from 13% to over 50% according to both the cause and the clinical and organizational setting where they are diagnosed. Despite direct muscle injury (i.e., traumatic rhabdomyolysis) remains the most common cause, additional causes, frequently overlapping, include hypoxic, physical, chemical or biological factors. The conventional triad of symptoms includes muscle pain, weakness and dark urine. The laboratory diagnosis is essentially based on the measurement of biomarkers of muscle injury, being creatine kinase (CK) the biochemical "gold standard" for diagnosis, and myoglobin the "gold standard" for prognostication, especially in patients with non-traumatic rhabdomyolysis. The essential clinical management in the emergency department is based on a targeted intervention to manage the underlying cause, combined with infusion of fluids and eventually sodium bicarbonate. We will present and discuss in this article the pathophysiological and clinical features of non-traumatic rhabdomyolysis, focusing specifically on Emergency Department (ED) management.

Contents

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1. Historical background

The first "reference" on rhabdomyolysis is thought to be found in the Pentateuch, the first five books of the Bible, which describes an episode of mass poisoning afflicting the Jews soon after the ingestion of quails caught during their staying in the Sinai desert ("*And while the flesh was yet between their teeth, ere it was chewed, the wrath of the Lord was kindled against the people, and the Lord smote the people with a very great plague*"; Numbers 11.33) [1]. The description is somehow consistent with rhabdomyolysis. It is well-known that during their spring migration across Northern Africa, quails can feed on large amounts of hemlock (*Conium maculatum*), a notoriously toxic herbaceous plant, the toxin of which (cicutoxin) typically causes rhabdomyolysis, usually associated with renal failure [2].

The second "reference" on rhabdomyolysis is probably associated with the description of the execution of Socrates by the Athenian state in 399 BCE. Despite Plato's dialogue "Phaedo" insinuates that Socrates may have died after drinking an extract of hemlock, doubts remain about the true nature of the poison. In fact, the major clinical findings reported in the Phaedo cannot be explained only by hemlock poisoning, and it seems more reasonable that the great philosopher died after drinking a mixture of poisons, probably including hemlock [3].

The third "reference", which actually represents the first medical description of the syndrome, is dated back to the early 1900s, describing the clinical pictures of survivors of the tremendous earthquake followed by a tsunami which destroyed Messina and Reggio Calabria in Southern Italy and caused >100.000 victims, on December 28, 1908. Three Authors, one German and two Italian surgeons, described almost at the same time the Crush syndrome, but only the Italian surgeon Antonino d'Antona reported the presence of shock and uremia associated with traumatic injuries [4–6].

The pathophysiological mechanisms, however, were first identified by Bywaters et al. in 1941, when the traumatic form of rhabdomyolysis was accurately described in the victims of the bombing of London. Myoglobin released from traumatized muscles was identified as the main substance responsible for kidney failure which, due to the lack of renal dialysis at that time, caused the majority of fatalities [7].

Traumatic rhabdomyolysis is extensively discussed in some excellent articles and reviews [8–10], and hence will not be treated in this article. Non-traumatic rhabdomyolysis represent a rapidly growing field of knowledge, as demonstrated by the increasing number of publications on this topic: >350 new articles have been published in 2016 (source: PubMed). We will present and discuss in this article the pathophysiological and clinical features of non-traumatic rhabdomyolysis, focusing specifically on the management in the Emergency Department (ED).

2. Definition and epidemiology

Although there is no consensus on the precise definition of this condition, the term rhabdomyolysis describes the rapid breakdown of striated, or skeletal, muscle. It is hence characterized by the rupture and necrosis of muscle fibers, resulting in release into the bloodstream and extracellular space of cell products. Since skeletal muscles comprises ~40% of body weight (i.e., several kg), and the destruction of just 100 g of muscle tissue is capable to induce the clinical syndrome of rhabdomyolysis, it is easy to understand that this "breakpoint" can be reached quite easily [11].

The precise knowledge on the actual incidence of rhabdomyolysis is limited, mainly due to the fact that many mild (i.e., oligo-symptomatic or asymptomatic) cases probably go unrecognized. Nevertheless, it has been reported that approximately 26.000 cases of rhabdomyolysis are hospitalized every year in the United States [12]. Rhabdomyolysis occurs with a wide spectrum of signs and symptoms, ranging from a completely asymptomatic increase of plasma creatine kinase (CK), through massive increases in blood levels of acute kidney injury (AKI) biomarkers, severe alterations of electrolyte balance and, in the most severe cases, disseminated intravascular coagulation (DIC) [9]. The literature evidence reports that the percentage of patients developing AKI secondary to rhabdomyolysis varies from 13% to over 50%, mainly depending on the clinical and organizational setting where it is diagnosed [9]. Notably, an important distinction should be made between the terms rhabdomyolysis, crush injury, compartment syndrome and crush syndrome [8,13]. The first term describes the damage to striated muscle cells or fibers; the second describes all those injuries occurring as consequence of crushing of bodily parts (usually a limb); the third describes the complications developing for increased pressure inside one or more muscular compartments (where rhabdomyolysis may, or may not, have occurred) which can cause interruption in the regional circulation and ischemic injury to nerves and muscles; the fourth describes the complex pathophysiological consequences caused by massive rhabdomyolysis, mainly involving both kidneys and coagulation system. There is frequent overlapping or subsequent evolution between the four aforementioned conditions. Others commonly used terms in this field are: i) myalgia, i.e., muscle ache or weakness without increases of CK, and ii) myositis, i.e., inflammatory process that includes muscle symptoms with increased CK activity. They both differ from rhabdomyolysis, which encompasses muscle symptoms associated with marked increases in CK [typically >5–10 times the upper limit of normal (ULN)] and often increased creatinine levels (usually accompanied with brown urine due to myoglobinuria) [14].

Interestingly, humans are not the only mammals affected by rhabdomyolysis. It has been demonstrated that up to 3% of exercising horses may be affected by this disorder, showing similar signs and etiologies [15].

3. Etiology

Direct muscle injury remains the most common cause of rhabdomyolysis, although the etiology includes up to four leading mechanisms, that are frequently overlapped: i) hypoxic, ii) physical, iii) chemical, iv) biological. Each one of these etiologic categories may have intrinsic or extrinsic causes, as follows (only citing the most frequent). *Hypoxic mechanisms*: i) extrinsic (carbon monoxide or cyanide poisoning), ii) intrinsic (compartment syndrome; compression; immobilization; vascular occlusion due to thrombosis or vasculitis). *Physical mechanisms*: i) extrinsic (trauma; burns; electrocution; hypo/hyperthermia); ii) intrinsic (exertion; seizures; status asthmaticus; agitation; malignant hyperthermia). *Chemical mechanisms*: i) extrinsic (environmental toxins, alcohol; drugs or substances of abuse); ii) intrinsic, mainly represented by electrolyte disorders (hypokalemia; hypophosphatemia; hypocalcemia; hypo/hypernatremia). *Biologic mechanisms*: i) extrinsic (infections from bacteria, viruses, parasite; preformed organic toxins); ii) intrinsic (dermatomyositis/polymyositis; endocrinopathies, mainly thyroid dysfunction) [16].

Road accidents are the most frequent direct traumatic causes, although entrapment in collapsed buildings poses the greatest challenge for emergency services due to the number of victims, which is often considerable. During some of the most recent catastrophes (i.e., the 1988 Armenian earthquake, and the 1999 earthquake which hit the Turkish region of Marmara) hundreds of victims required hemodialysis. Notably, hospitals are usually impacted by the earthquakes, since they can be at least in part damaged or even completely destroyed. After the earthquake in Kobe Japan) in 1995, 42–69% of the local hospital personnel was unavailable, either because direct victim or unable to travel due to collapsed roads [10]. It is now well recognized that late mortality in earthquake victims is primarily due to crush syndrome complicated by acute kidney injury (AKI) [9,10]. A frequent mechanism causing rhabdomyolysis is prolonged compression during immobility. This is usually due to stroke in elderly patients, time consuming surgery without adequate periodic patient mobilization, self-induced intoxication (with the concomitant effects of immobilization and toxicity from

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