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A Mini-Review of Uncommon Causes of Rhabdomyolysis and a New Proposed Treatment

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Abstract

Background: Rhabdomyolysis is a syndrome of muscle breakdown with the release of intramuscular components into the bloodstream. It has various causes, and recognizing rare causes is of utmost importance.

Methods: We completed three searches in the PubMed (Medline) database for articles on Rhabdomyolysis. Specifically, each retrieved article included Rhabdomyolysis, and one of the following terms appeared in both the title and the abstract: atypical presentations, diagnosis, barriers, and challenges.

Discussion: COVID-19 infection-induced Rhabdomyolysis is an initial or late presentation of the disease recognized during the pandemic. Viral illness-induced Isolated myositis can cause severe Rhabdomyolysis. Myositis secondary to Crohn's disease can manifest as Rhabdomyolysis despite being a rare presentation. Baking Soda-induced severe hypokalemia is recognized as a cause of Rhabdomyolysis. Eating Quail as the cause should be thought of in the proper context. The proposed additional treatment for rhabdomyolysis, especially in recurrent forms, can consist of corticosteroids, which need further investigation.

Conclusion: It is of great importance for clinicians to recognize uncommon causes and presentations of Rhabdomyolysis to start treatment earlier in the hope of curbing the dreaded complications like AKI. Newer additional therapies should be investigated.

Keywords: Rhabdomyolysis • Uncommon causes • Additional therapies • Hypokalemia

Introduction

Rhabdomyolysis is a syndrome of muscle breakdown with the release of intramuscular components into the bloodstream. It ranges from an incidental finding of elevated Creatine Phosphokinase (CPK) without any symptoms to Acute Kidney Injury (AKI), electrolyte disturbances, and Disseminated Intravascular Coagulation (DIC) [1]. The leading causes are muscle injury by direct trauma or other causes, including specific drugs or toxins, some electrolyte disturbances, heat stroke, genetic diseases, and conditions like Neuroleptic Malignant Syndrome (NMS) and malignant hyperthermia [2]. In literature, the prevalence of typical presentation with a triad of myalgia, weakness, and myoglobinuria is reported to be less than 10%. More than 50% of patients do not present with myalgia, and the only presentation is colored urine [2,3]. The primary laboratory abnormality in Rhabdomyolysis is elevated CPK. It starts rising within two to twelve hours after muscle injury happens and peaks within twenty-four to thirty-three hours, with a decline within seven days; however, with continued muscle injury or adverse effects of the disease, for example, Compartment syndrome, this timeline may change [1,4]. The primary treatment for Rhabdomyolysis includes monitoring electrolyte disturbances, including hyperkalemia, hypocalcemia, hyperphosphatemia, and Intravenous (IV) hydration. More importantly, diagnosing at-risk patients with elevated levels of CPK above 5000 U/L early in the course of the disease and implementing preventive measures with aggressive and early volume replacement to curb AKI is of utmost importance [5]. The choice and the rate of intravenous fluid therapy and the use of Bicarbonate need to be well-established in the literature [6,7]. A case of a middle-aged black woman with rhabdomyolysis is reported that was caused by intense shivering chills and rigor from pneumonitis in 2022. She had a rise in CPK to 200,000 U/L along with AKI. She was treated with intravenous fluid plus sodium bicarbonate and hemodialysis with progressive improvement in kidney function that took up to seven weeks to full recovery [8]. Often, the diagnosis is made during the evaluation of renal dysfunction or the presence of discoloring of urine; therefore, recognizing common and uncommon or rare causes could help with earlierdiagnosis and treatment. In this mini- review, we

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looked at the reported unique, unusual, and rare causes of Rhabdomyolysis in the literature.

Literature Review

Methods

A comprehensive search of PubMed (Medline) was performed to identify articles with Rhabdomyolysis in the abstract or medical subject headings, which resulted in 11620 articles. Subsequent searches for articles were performed by including the words: "rare, uncommon, unusual, atypical, barrier, diagnostic, or challenges," which resulted in 41 eligible articles, including 24 articles with atypical presentations of Rhabdomyolysis, nine articles with diagnostic challenges, and eight articles which were identified using the keywords of unusual, atypical, or uncommon.

The first and second authors independently reviewed 41 articles' texts or abstracts, excluding 30 articles not identified as uncommon, unusual, atypical, or with diagnostic or treatment challenges. This screening led to 11 articles that met all criteria. Authors used the comprehensive list of causes mentioned in UpToDate [9], a review article by Torres, et al., [3], and the other medical causes of Rhabdomyolysis by Allison and Bedsole [10] to exclude common causes and presentations and include rare or unusual causes of Rhabdomyolysis.

Review

Eleven articles are divided into three main categories regarding the causes of rhabdomyolysis: Infection, autoimmune disease, and toxins/drugs.

Infection

COVID-19: There is a case report with severe rhabdomyolysis in a 51-year-old male patient with COVID 19 infection who presented to the ER with myalgia, dry cough, and chills. His lab results showed a CPK of 339,500 U/L. He did not report any strenuous exercise, and his urine drug test was negative. He developed Acute Kidney Injury (AKI), ending up with the need for hemodialysis at the time of discharge. It was one of the first COVID-19 cases outside of China reported to have severe rhabdomyolysis as the primary presenting feature of COVID-19 [11]. Another case of rhabdomyolysis was reported in a 60-year-old man with COVID-19 who was admitted to the hospital with a fever and cough and had new leg pain and weakness. He was found to have rhabdomyolysis on day 9 of hospitalization with a CPK level of 11,842 U/L. This case reported Rhabdomyolysis as a late manifestation of COVID-19 [12].

Isolated myositis related to influenza: Agrawal, et al., reported a case of a 36-year-old male presented to the hospital with three days of fever and isolated left upper extremity weakness, swelling, and erythema. Initial labs showed AKI along with a CPK of 81,089 U/L. X-ray of the shoulder and computed tomography scan showed soft tissue edema. The patient tested positive for influenza type A H1N1 [13].

Autoimmune disease

Crohn's disease: A 43-year-old male without significant past medical history who was admitted to the hospital with right upper extremity weakness, dysphagia, and melena, reported to have a CPK level of 50,000 U/L with elevated liver function testing and negative urine drug testing. There were no other causes for Rhabdomyolysis other than myositis based on a nerve conduction study (EMG-NCV) with the negative autoimmune panel. The patient responded well to corticosteroids. Colonoscopy and biopsy showed Crohn's disease [14].

Toxins/drugsa

Baking soda: Severe hypokalemia is a known cause of Rhabdomyolysis, but baking soda causing Rhabdomyolysis is not a common cause in literature. Scolarli and Myles reported a case of a 35 y.o woman at 37 weeks of gestation admitted with worsening weakness who showed runs of ventricular tachycardias and was found to have an average troponin level but CPK of 7,971 U/L along with a potassium level of 2.1 mg/dl. She had an echocardiogram done that showed a low EF of 30% and was diagnosed with postpartum cardiomyopathy as well [15]. Another case of Baking Soda Pica was reported in which a young woman at 31 weeks of pregnancy, presenting to the hospital with worsening weakness with severe hypokalemia and ensuing severe Rhabdomyolysis [16].

Quail poisoning: Three cases of Rhabdomyolysis which started 3-8 hours after eating fresh roasted Quail showed other rare causes of rhabdomyolysis. The main presenting symptom for these patients was myalgia, with a range of CPK from 1520 U/L to 11,000 U/L. In all three cases, no other causes were found. All three cases responded well to IV hydration [17].

Proton Pump Inhibitors (PPIs): Altebainawi, et al., identified 57 rhabdomyolysis cases associated with PPIs use in FAERS system based on spontaneous reports submitted between 2013 and 2021. They showed the association between rhabdomyolysis and PPI use in reports [18].

Azithromycin: Rhabdomyolysis can be triggered by Azithromycin alone. A 17-year-old patient attended the emergency department due to generalized myalgia. CK was found to be significantly high. He reported taking Azithromycin 500 mg, 2 days before his symptoms, prescribed by his primary care physician due to fever, abdominal pain, nausea, and vomiting. He had no significant past medical history, however there was a positive family history for polymyositis in one of his uncles. He reported doing exercise regularly for the last 1.5 years with no events. He was instructed to discontinue Azithromycin and he received intravenous fluid. After two days, the symptoms resolved and CK declined [19].

Discussion

Rhabdomyolysis is classified into three main categories: Traumatic, non-traumatic exertional, and non-traumatic non-exertional [9] (Table 1). Infectious organisms, including bacteria, viruses, parasites, and fungi, are among the non-traumatic, non-exertional causes of rhabdomyolysis. Influenza virus and HIV are

the most common viral etiologies [20]. The primary proposed Rhabdomyolysis mechanism includes direct viral or bacterial invasion of skeletal muscle or toxin generation, especially in septic conditions [20]. It is of utmost importance to understand the relationship between various infectious causes and the risk of Rhabdomyolysis, as prompt treatment may reduce the risk of fearsome complications such as AKI. COVID-19 infection has been recognized as a new viral illness causing Rhabdomyolysis as an initial and late disease presentation [12]. Before the COVID-19 pandemic, reports of Rhabdomyolysis with Severe Acute Respiratory Syndrome (SARS) occurred in Taiwan [21]. Apart from the proposed mechanism for Rhabdomyolysis in infectious etiologies, elevated inflammatory markers and cytokine release have been proposed as extra mechanisms in COVID-19 and SARS infections [12] Viral illnesses, especially Influenza, as one of the most common viral causes, can manifest with severe Rhabdomyolysis and AKI with only an isolated form of myositis with involvement of one extremity [13]. Increased awareness of clinicians is required to recognize this clinical picture. Myositis is a known cause of Rhabdomyolysis. The leading causes of myositis include inflammatory myositis, dermatomyositis, and polymyositis, or statin-related [1]. However, myositis is a rare extraintestinal manifestation of Crohn's disease. Muscular symptoms, especially myalgia and CPK levels, are suggested to be monitored in this patient population [22]. It should be emphasized then to be aware of this consequence of myositis in Crohn's disease as a manifesting symptom and to check CPK levels (Table 1).

Traumatic/Direct injury
Trauma (Crush syndrome, motor vehicle accidents, immobilization)
Compartment syndrome
Arterial occlusion (prolonged T ourniquet or surgical vascular clamping)
Non-traumatic exertional
Strenuous Exercise
Heat stroke or severe hypothermia
Genetic disorders (glycolysis, glycogenolysis, lipid metabolism disorders, Mitochondrial myopathies, or other genetic disorders)
Immune-mediated myopathies (Polymyositis, Dermatomyositis)
Malignant hyperthermia
Neuroleptic malignant syndrome
Non-traumatic non-exertional
Toxins (Alcohol, Cocaine)
Prescription drugs (Statins, Fibrates, Psychoactive drugs)
Infectious causes
Electrolyte disturbances
Endocrine disorders
Miscellaneous and other causes

Table 1. Common causes of rhabdomyolysis.

Metabolic derangements and electrolyte disturbances, especially hypokalemia, are recognized as a cause of Rhabdomyolysis. Apart from the leading known causes of Hypokalemia, like diuretic use, baking soda use in pregnancy as a manifestation of Pica could also result in Rhabdomyolysis and severe hypokalemia [15,16]. The massive use of baking soda could result in metabolic alkalosis and ensuing hypokalemia that exceeds the kidneys' capacity to compensate for this bicarbonate load. Hypokalemia destabilizes cell membranes and alters muscular blood flow with further cell breakdown [16]. Coturnism is a rare cause of Rhabdomyolysis that happens with eating Quail, Coturnix coturnix, during the migration period of this bird in Autumn in the Mediterranean area. The cooking method does not affect the toxin. Symptoms start around 1-9 hours after digestion. The toxin is in the seeds of some plants eaten by birds, which have Nicotineic effects on autonomic ganglia. However, some unknown genetic background seems to play a role, as not all affected family members develop the symptoms in the reviewed case reports [17]. PPI-associated rhabdomyolysis is rare; however, due to the significant utilization of PPIs, physicians and patients are highly recommended to be well-informed about the increased risks of rhabdomyolysis associated with PPIs. CYP2C19-mediated metabolism of PPIs and inhibition of CYP3A4 inhibition are thought to cause clinically significant interactions with statins, augmenting the risks of rhabdomyolysis. However, the mechanisms causing rhabdomyolysis are not completely expounded [18].

Azithromycin has been reported to be one of the rare causes of rhabdomyolysis when used with combination of other drugs particularly cyclosporin or statins. However, clinicians must be aware that rhabdomyolysis can be triggered by Azithromycin alone and particularly if there is a positive family history for neuromuscular disorders [19]. The primary treatment for Rhabdomyolysis and secondary AKI is intravenous fluid. The fluid type and administration rate are not well known [7]. Bicarbonate and Mannitol are an area of debate, and extreme caution and monitoring are needed when using this additional potential treatment [6,7]. Dexamethasone has anti-inflammatory and immunosuppressive properties, and the use of this drug in cases of Rhabdomyolysis showed some promising results based on case reports [23]. Summerlin et al. reported a case of an African American 13-year-old patient with three episodes of Rhabdomyolysis due to strenuous activity without any proven genetic abnormality. The first episode was managed as an inpatient with IV hydration with an average drop in CPK of 0.6% per hour; the second episode, which happened two and a half months after the first episode, was managed concomitantly with Dexamethasone with a dose of 16 mg oral for three days in the hospital with a tapering regimen of 5 days (8 mg for three days, 4 mg for one day and 2 mg for one day) after discharge. The average drop in CPK was 2.5% per hour after initiating Dexamethasone. The third attack was managed as an outpatient therapy with only Dexamethasone 4 mg twice a day for three days, along with oral sports drink hydration of up to 2 liters per day [23]. There are six other case reports that Summerlin, et al., summarized in their report in whom corticosteroid administration in rhabdomyolysis without a proven genetic etiology (especially Lipin-1 deficiency) showed positive effects on the treatment along with conventional therapies (Rhabdomyolysis caused in these cases reported to be due to Cytomegalovirus (CMV) [24], heat stroke [25], intoxication with 3,4- Methylenedioxy-Methamphetamine (MDMA) or 'ecstasy,' alcohol-induced [26].

Conclusion

Apart from the common causes of Rhabdomyolysis encountered more commonly, clinicians should be aware of the other known and unknown causes of Rhabdomyolysis. This awareness could help further investigate newer causes of this

detrimental condition. More uniquely proposed treatments like corticosteroids should be considered in the proper context. Further research and studies are needed in the treatment of Rhabdomyolysis.

Limitations

The case report-based nature of this mini-review could affect the accurate estimate of the importance of the findings. Our review, with our best intentions, might have inadvertently excluded some of the relevant publications.

Conflict of Interest

No financial interest or any conflict of interest exists.

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