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Rhabdomyolysis Caused by Hypothyroidism: Research Progress

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ABSTRACT

Rhabdomyolysis (RM) refers to the clinical syndrome caused by the release of intracellular substances into the extracellular fluid and blood circulation after rhabdomyocyte destruction due to various etiologies. In severe cases, RM can lead to life-threatening conditions such as acute kidney injury. Hypothyroidism is a rare cause of RM that can lead to missed diagnosis or misdiagnosis, and the condition worsens in the absence of timely and effective treatment. Herein, reported cases of RM caused by hypothyroidism are summarized, and clinical diagnosis and treatment recommendations are proposed to facilitate early identification and treatment of the disease.

Rhabdomyolysis

Rhabdomyolysis (RM) is a syndrome in which lysis and destruction of rhabdomyocytes are caused by various factors, and the release of various substances into the bloodstream, such as intracellular creatine kinase (CK) and myoglobin, causes biochemical disorders and organ functional impairment [1]. The disease severity can range from asymptomatic elevation of serum CK to life-threatening conditions such as electrolyte imbalance and acute kidney injury (AKI) [2]. When RM occurs, skeletal muscle is destroyed, causing the release of intracellular substances (such as potassium ions, purines, myoglobin, aspartate aminotransferase, lactate dehydrogenase, aldolase, and CK) into the extracellular fluid and blood circulation [3], which can lead to a series of complications.

The clinical manifestations of RM are diverse, but at onset, patients can develop the classic triad of myalgia, muscle weakness, and dark urine [4]. Muscle pain is the most common symptom of RM, occurring in approximately 50 % of patients, and dark urine occurs in 30–40 % of patients [5]. Patients can also present with atypical symptoms such as fatigue, edema, fever, nausea, vomiting, and even mental disorders. Fewer than 10 % of patients exhibit the classical triad, and up to 50 % of patients do not have any symptoms [6]. RM can also cause a range of complications, including renal failure, hypovolemia, cardiac arrhythmias, osteofascial compartment syndrome, severe electrolyte disturbances, and diffuse intravascular coagulation [7, 8]. When these severe complications occur in combination, the mortality rate increases significantly. AKI is one of the most common complications of RM, with an incidence of 13–50 % [9].

The history of RM can be traced back to biblical times. When the Israelites left Egypt, they ate quail poisoned by celery and developed symptoms similar to RM [10]. At that time, RM was not a known condition. In 1916, the German surgeon Ludwig Franken-

thal reported the first case of RM and AKI caused by trauma in the 20th century [10]. During the same period, official German military medical records documented as many as 126 RM cases, but this fatal syndrome did not attract much attention at that time [10]. During World War II, after the London bombings, Bywaters and Beall described this syndrome in detail [11]. Also at that time, RM was officially recognized. Since then, an increasing number of cases of RM-induced AKI have been reported [12, 13].

RM leads to AKI through a variety of mechanisms. During RM, much myoglobin is released into the circulation. The mechanisms of myoglobin-induced AKI are as follows: (1) renal vasoconstriction; (2) an increase in the myoglobin concentration in the renal tubules due to water reabsorption, eventually forming a plaque and resulting in renal tubular blockage; and (3) direct cytotoxic effects of myoglobin in the renal tubules. Myoglobin degradation produces free iron ions, which can release free electrons, further aggravating cell damage [14, 15]. However, the sensitivity of myoglobin as a diagnostic marker of RM is poor; an increase in CK levels is considered a sensitive indicator of RM. The likelihood of AKI in RM patients is directly related to the degree of increase in CK [15].

Unless it is highly suspected, RM is easily overlooked because individuals often have no obvious clinical symptoms or present atypical clinical manifestations. Therefore, a definitive diagnosis of RM should be established through laboratory testing. Clinically, RM can be diagnosed when an individual has a serum CK level greater than 5 times the normal limit or greater than 1000 U/l. Analyses of serum myoglobin, urine (myoglobinuria), and metabolic indicators, including serum creatinine and electrolytes, are also important [8, 16]. Biochemical indicators can change in patients with early-stage RM. Serum CK starts increasing within 2–12 hours after muscle injury and peaks within 1–3 days. In the absence of sustained muscle injury, CK will gradually decrease within 3–5 days; the rate of decrease is approximately 39 % of that on the previous day [3, 16], depending on the extent of the damage and the effectiveness of treatment [16]. When renal function is impaired, blood urea nitrogen, creatinine, serum myoglobin, and urinary myoglobin become elevated. A urine occult blood test can be positive without any red blood cells on microscopic examination. Half of RM patients had high troponin I, 58 % of whom were eventually found to have true-positive results, while 33 % had false-positive results, and 9 % had indeterminate positive results [17]. Other abnormalities caused by RM include electrolyte disorders. The most common electrolyte abnormalities are hyperkalemia and hyperphosphatemia [18]. The severity of hyperkalemia and hyperphosphatemia is related to the reduction in the effective circulating volume, which further promotes the occurrence of AKI. RM histopathological results usually include the loss of nuclei and muscular stria and the disappearance of inflammatory cells. Muscle biopsies can be done but are not required to diagnose RM [19].

The etiology of RM can be divided into two categories: traumatic factors and nontraumatic factors. Traumatic factors include excessive exercise, squeezing, explosions, electric shock, etc. [5]. One study showed that in 85 % of critically ill patients admitted to the intensive care unit for trauma, some biochemical evidence (abnormal CK) of RM was observed [20]. Nontraumatic factors are more common. They include drugs (statins, fibrates, colchicine, corticosteroids, etc.), endocrine diseases (diabetes, thyrotoxicosis, hypothyroidism, etc.), electrolyte abnormalities (hypophosphatemia, hypokalemia, hypocalcemia, etc.), poisoning (food, carbon monoxide, paraquat, and other toxicants), various viruses (influenza A and B, Coxsackie virus, herpes simplex virus, parainfluenza virus, adenovirus, Echovirus, human immunodeficiency virus, etc.), bacterial infections (streptococcus, salmonella, legionella, staphylococcus, etc.), and hereditary and autoimmune diseases (polymyositis and dermatomyositis) [5, 10]. The most common causes of RM in adults are trauma, immobilization, sepsis, and cardiovascular surgery, while in pediatric patients, the most common causes are viral myositis, trauma, connective tissue diseases, exercise, and drug overdose [5, 21]. As many as 5–10 % of RM cases may not have a clear cause [5].

Hypothyroidism

Hypothyroidism is a systemic hypometabolic syndrome caused by reduced synthesis and secretion of thyroid hormones or weakened tissue function. Depending on the severity, hypothyroidism is categorized as either overt or subclinical. The prevalence of hypothyroidism varies widely between populations and is related to thyroid-stimulating hormone (TSH) cutoff values, sex, age, and ethnicity, among other factors. A lower TSH cutoff value corresponds to a higher prevalence. In the United States, the prevalence of hypothyroidism is approximately 4.6 %, of which 4.3 % of cases are subclinical hypothyroidism, with no obvious clinical manifestations, and 0.3 % are cases of clinical hypothyroidism [22]. In China, the overall prevalence of hypothyroidism is 17.8 %, the prevalence of subclinical hypothyroidism is 16.7 %, and the prevalence of clinical hypothyroidism is 1.1 % [23]. The etiology of hypothyroidism is complex. Globally, environmental iodine deficiency is the most common cause [24]. In areas where iodine is abundant, such as the United States, the most common cause of hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's thyroiditis). Thyroid surgery, treatment of hyperthyroidism with iodine-131, and pituitary or hypothalamic tumors can also contribute to the development of hypothyroidism [22]. The diagnosis of hypothyroidism mainly relies on laboratory tests combined with clinical symptoms, signs, and medical history. Primary hypothyroidism can be diagnosed based on increased serum TSH and reduced free thyroxine (FT4); subclinical hypothyroidism can be diagnosed based on increased serum TSH and normal FT4. If thyroid peroxidase antibody (TPOAb) and/or thyroglobulin antibody (TGAb) are positive, the hypothyroidism can be considered autoimmune thyroiditis [25].

The disease has an insidious onset and a long course, and many patients lack specific symptoms and signs. The main symptoms are a decreased metabolic rate and diminished sympathetic excitability. Typical symptoms often do not appear for months or even years. Chills, fatigue, swelling of the hands and feet, lethargy, memory loss, hypohidrosis, joint pain, increases in body weight, constipation, menstrual disorders or menorrhagia, infertility, etc., are common manifestations [26, 27]. Approximately 79 % of patients with hypothyroidism have muscle symptoms such as myalgia, proximal muscle weakness, and spasms, though severe muscle involvement is very rare [23, 28, 29].

RM Caused by Hypothyroidism

Musculoskeletal involvement in hypothyroidism has been recognized for many years [30]. However, in the traditional view, hypothyroidism is not a cause of RM. In 1979, Halverson reported a case of hypothyroidism with renal failure caused by a large amount of muscle necrosis and myoglobinuria. The authors proposed that RM should be considered a clear but rare complication of hypothyroidism [29]. Later, Riggs et al. [31] and Sekine et al. [32] reported cases of RM caused by hypothyroidism and proposed that hypothyroidism is one of the causes of RM and that hypothyroidism should be excluded in all patients with elevated CK levels. Janjua et al. also proposed that hypothyroidism should be used for the differential diagnosis of RM [4]. The American Thyroid Association clinical practice guidelines recommend that patients with elevated serum CK and/or elevated lactate dehydrogenase levels be screened for hypothyroidism for at least 2 weeks [27].

The exact etiology of RM caused by hypothyroidism is not clear [33]. The active form of thyroid hormone is triiodothyronine (T3), which plays a key role in maintaining muscle function and integrity. The main fuel substrate for muscle energy metabolism is glycogen. T3 can promote carbohydrate metabolism and increase the mobilization and utilization of glycogen in muscle tissue. Muscle contraction and relaxation mainly rely on adenosine triphosphate (ATP) hydrolysis and the energy produced by the mitochondrial respiratory chain, which can be regulated by T3. T3 also affects myosin filaments and muscle. Therefore, the most popular current hypothesis is that hypothyroidism leads to RM; that is, during hypothyroidism, T3 production, glycogen utilization, ATP hydrolysis, and mitochondrial activity decrease, so the energy required for muscle contraction and relaxation is lacking, leading to a series of metabolic dysfunctions [34]. Thyroid hormone deficiency leads to glycogenolysis, mitochondrial oxidative metabolism, and abnormal triglyceride turnover, which in turn lead to the transformation of fast-twitch (type II) muscle fibers into slow-twitch (type I) muscle fibers, decreased actin–myosin contractility, decreased myosin ATPase activity, and decreased ATP conversion rates in skeletal muscle, resulting in insufficient muscle perfusion, hypoxia in muscle tissue, and reduced muscle energy storage [35–37].

RM caused by hypothyroidism is very rare, and there are many predisposing factors contributing to its development, such as the use of statins, trauma, strenuous exercise, alcohol consumption, and illicit drug use. Drug nonadherence is also a predisposing factor for the occurrence of RM in patients with hypothyroidism [4, 33, 38]. Drug nonadherence is a common problem, with an incidence of up to 25–50 % [15, 39]. Ghayur et al. reported a case of RM caused by nonadherence to thyroxine drug treatment in a hypothyroidism patient; the nonadherence eventually caused AKI, requiring the patient to undergo hemodialysis for 4 weeks. The authors proposed that irregular levothyroxine drug treatment in hypothyroidism patients may be a cause of RM-induced AKI [15]. Another case report detailed RM caused by fluctuations in the patient's condition resulting from an improper diet. Manappallil et al. described a patient with Hashimoto's thyroiditis who experienced hypothyroidism and RM after consuming raw broccoli and proposed that diet was involved in hypothyroidism. Foods such as kale, Brussels sprouts, cauliflower, and cabbage contain goiter-causing chemicals. The intake of these foods in large amounts can cause or aggravate thyroid dysfunction, but most of these goiter-causing chemicals are inactivated when foods are cooked [37]. Although these patients have many predisposing factors, some case reports indicate that the occurrence of RM may not be related to obvious predisposing factors [4, 38, 40, 41]. Therefore, an RM diagnosis cannot be based on whether a predisposing factor is identified in clinical practice. Most patients have RM in the context of a history of hypothyroidism, but in rare cases, no history of thyroid disease is reported. If RM is the first symptom, the likely outcome is a missed diagnosis or misdiagnosis [38, 41]. Salehi et al. summarized 10 previously reported cases of RM caused by hypothyroidism in adults. In one patient, subclinical hyperthyroidism was induced by taking propylthiouracil, and five other patients had no previous history of thyroid disease. Six patients had no risk factors for RM [33].

Patients with RM due to hypothyroidism have elevated serum CK and myoglobin levels [41]. However, no clear correlation has been identified between hypothyroidism severity and CK levels [15]. Although these patients may have combined hypothyroidism and RM-related signs and symptoms, compared with the pathogenesis of other diseases, the onset of RM caused by hypothyroidism is more insidious, and as mentioned above, up to 50 % of RM patients have no obvious symptoms. Therefore, its diagnosis is easily missed. Patients with hypothyroidism have decreased endurance and may experience chest tightness and other discomfort when pericardial effusion is present, and at this time, if an abnormal myocardial enzyme profile is noted, cardiac causes are easy explanations, leading to misdiagnosis.

The strategy for RM treatment is to eliminate the cause as soon as possible, provide a large fluid infusion to promptly alkalize the urine, and provide symptomatic treatment (e. g., antioxidation and anti-infection) concurrently to prevent and treat serious complications such as AKI [34]. All patients should undergo a fluid infusion at the beginning of treatment and repeat it until the laboratory results confirm that CK levels are no longer increasing. The best type of fluid for infusion and the rate of infusion are unknown. The most commonly used are lactated Ringer's solution and saline solution (0.9 % or 0.45 %) for initial fluid resuscitation to maintain renal perfusion and thus minimize renal injury. The guidelines state that there are no randomized controlled trials comparing lactated Ringer's solution with saline (0.9 % or 0.45 %), so it is not clear which type of fluid is better. Therefore, in the treatment of rhabdomyolysis, the use of either is acceptable, and the specific one can be chosen by the attending physician. Further research is needed in this area. Real-time monitoring of urine output is required to adjust the rate of infusion while treatment is being administered. Initial infusion is recommended at a rate of 400 ml/hour, with urine output best maintained at 1–3 ml/kg/hour over the course of treatment [16]. Fluid infusion should be continued until CK drops lower than 5000 U/l; RM patients with CK levels less than 5000 U/l have a lower risk of AKI. For many years, CK level has been considered a predictive factor for the occurrence of AKI, and a CK level greater than 5000 U/l is correlated with high risk of AKI but is not related to AKI severity [20, 38, 42].

When AKI occurs, blood purification should be performed in a timely manner to correct electrolyte imbalances, improve water

and sodium retention, and reduce serum CK, myoglobin, serum creatinine, urea nitrogen, and cytotoxins. Renal replacement therapy is an important and effective treatment method. If serum creatinine increases to 3 times the baseline value or reaches 353.6 µmol/l, if the urine output is less than 0.3 ml/kg/h over 24 hours, or if the patient has no urine output for 12 hours, renal replacement therapy should be started [43]. This treatment is recommended because continued aggressive fluid resuscitation in the absence of renal clearance may instead lead to volume overload and endanger the patient's life.

After levothyroxine treatment, free triiodothyronine (FT3), FT4, and TSH levels in patients with RM caused by hypothyroidism reportedly returned to normal, and the CK level decreased. During levothyroxine treatment, TSH and FT4 should be measured every 4–6 weeks to evaluate the treatment effects. If TSH remains above the reference range, the dose of levothyroxine can be increased by 25–50 µg/day until the treatment goal is reached [38]. After fluid infusion and symptomatic treatment, if the primary disease improves, CK levels should return to normal [38]. Therefore, timely thyroxine supplementation and symptomatic support are keys to treatment. Delayed diagnosis leads to a series of serious complications of RM, such as AKI and severe metabolic disorders that require renal replacement therapy, and further progression of the disease requires a higher level of care and mechanical ventilation [44].

Alongside timely and effective diagnosis and treatment, RM prevention is very important. The following aspects should be considered: an appropriate amount of exercise, adequate hydration, avoiding the combined use of drugs that cause muscle damage, and avoiding a high-temperature environment and high-intensity physical work. Severe hypokalemia can reduce muscle blood flow, leading to muscle spasms, ischemic necrosis, and RM, in addition to reduced energy production during muscle contraction and reduced myocyte membrane transit potential during hypokalemia, leading to muscle damage. Therefore, some studies have reported that when hypokalemia occurs, the primary disease should be treated promptly, the hypokalemia should be corrected, and relevant indicators, for example, muscle enzymes, should be monitored [45–47]. Severe hyponatremia can also lead to RM; although the exact pathogenesis is not clear, screening for RM should not be neglected when severe hyponatremia is present [48].

Conclusion

RM caused by hypothyroidism is a rare but serious disease. Critically ill patients may develop severe electrolyte disorders, AKI and other complications, and even life-threatening conditions. Prompt recognition and effective treatment can lead to complete recovery, so early diagnosis and timely treatment of RM are essential for early recovery from and prevention of potentially fatal complications.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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