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Rhabdomyolysis featuring muscular dystrophies

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ABSTRACT

Background: Rhabdomyolysis is a potentially life threatening condition of various etiology. The association between rhabdomyolysis and muscular dystrophies is under-recognized in clinical practice.
Objective: To identify muscular dystrophies presenting with rhabdomyolysis at onset or as predominant feature.
Methods: We retrospectively reviewed clinical and laboratory data of patients with a genetically confirmed muscular dystrophy in whom rhabdomyolysis was the presenting or main clinical manifestation.
Results: Thirteen unrelated patients (males = 6; females = 7) were identified. Median age at time of rhabdomyolysis was 18 years (range, 2–47) and median duration between the first episode of rhabdomyolysis and molecular diagnosis was 2 years. Fukutin-related protein (*FKRP*) muscular dystrophy (n = 6) was the most common diagnosis, followed by anoctaminopathy-5 (n = 3), calpainopathy-3 (n = 2) and dystrophinopathy (n = 2). Four patients experienced recurrent rhabdomyolysis. Eight patients were asymptomatic and 3 reported myalgia and exercise intolerance prior to the rhabdomyolysis. Exercise (n = 6) and fever (n = 4) were common triggers; rhabdomyolysis was unprovoked in 3 patients. Twelve patients required hospitalization. Baseline CK levels were elevated in all patients (median 1200 IU/L; range, 600–3600).
Conclusion: Muscular dystrophies can present with rhabdomyolysis; *FKRP* mutations are particularly frequent in causing such complication. A persistently elevated CK level in patients with rhabdomyolysis warrants consideration for underlying muscular dystrophy.

1. Introduction

Rhabdomyolysis is a potentially life threatening condition due to acute myofiber necrosis, characterized by a marked elevation in serum creatine kinase (CK) levels with or without myoglobinuria [1,2]. Myoglobinuria indeed may go undetected if rhabdomyolysis is mild or urine myoglobin does not exceed 100 mg/dl [2]. The clinical presentation is variable with a combination of myalgia, muscle swelling and acute onset muscle weakness. Acute renal failure is the most serious complication occurring in approximately 15% to 50% of cases [3]. The etiologies of rhabdomyolysis are various and include acquired and inherited causes; genetic predisposition and environmental factors may be contributing factors. An isolated episode of rhabdomyolysis in an otherwise healthy individual, in the context of a clearly identifiable exogenous (e.g. drugs, trauma or infections [2,4,5]) or endogenous trigger (e.g. hypothyroidism [2]), may require no further diagnostic evaluation. Conversely, recurrent rhabdomyolysis, a history of preexisting symptoms such as exercise intolerance, exercise-induced muscle cramps, muscle weakness, or positive family history of myopathy are all concerns for an inherited muscle disorder [2,6].

Recurrent rhabdomyolysis is the hallmark of many metabolic myopathies in which rhabdomyolysis is often precipitated by exercise or fever and followed by complete clinical recovery [2,6,7]. CK values may normalize in between episodes of rhabdomyolysis [e.g. in carnitine palmitoil transferase 2 (CPT2) deficiency] or may persist elevated (e.g. in myophosphorylase deficiency, McArdle disease) in metabolic myopathies [6,7]. Rhabdomyolysis can also be a manifestation of the skeletal muscle ryanodine receptor 1 (RYR1) defect, often but not necessarily, occurring in the setting of malignant hyperthermia [2]. Progressive muscle weakness, muscle atrophy and persistently elevated CK values are classic features of muscular dystrophies. However, rhabdomyolysis can occur also in patients with muscular dystrophies and be precipitated by exercise or other etiologies, similarly to what observed in individuals with other types of myopathies [8–10]. Less frequently, rhabdomyolysis occurs spontaneously with no identifiable trigger in muscular dystrophies, or may be the initial manifestation of it in asymptomatic or mildly symptomatic patients [11–17].

The association between rhabdomyolysis and muscular dystrophies is less well recognized in clinical practice than the association between rhabdomyolysis and metabolic myopathies. This often leads to the misdiagnosis of metabolic myopathy or to delayed diagnosis, especially in the absence of anatomical footprint on muscle biopsy. For example, in a large retrospective study with 475 patients manifesting rhabdomyolysis, muscular dystrophy was suspected only in one patient on the basis of the muscle biopsy findings and was not confirmed genetically [4]. The

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unusual association between muscular dystrophy and rhabdomyolysis, frequently described in the form of case reports, could be due to the rarity or under-recognition of this phenomenon.

The aim of this study is to identify the most frequent muscular dystrophies presenting with rhabdomyolysis at onset or having rhabdomyolysis as predominant feature.

2. Materials and methods

The Institutional Review Board of Mayo Clinic approved this study. An electronic record retrieval system was used to identify retrospectively patients evaluated by neuromuscular specialists at our institution between 1997 and 2014 for one or more episodes of rhabdomyolysis and whose evaluation confirmed a diagnosis of muscular dystrophy either through genetic testing, immunohistochemical analysis of muscle tissue or both. We searched the electronic medical records for the terms rhabdomyolysis and muscular dystrophy and the matching CPT codes.

2.1. Inclusion criteria for rhabdomyolysis

An episode of rhabdomyolysis was defined as acute elevation of serum CK level of about 10× above the baseline, associated with acute onset of one or more of the following clinical features: muscle pain and swelling, muscle weakness, significant worsening of preexisting weakness, myoglobinuria, followed by clinical improvement and return of the CK levels to baseline [1]. The criteria for rhabdomyolysis we used were in agreement with the current literature [1,2]. For patients with no available laboratory data during an episode of presumed rhabdomyolysis or physician's note documenting the rhabdomyolysis, this was considered likely if there was a clear history of *Coca-Cola-like* color urine suggestive of myoglobinuria, in addition to one or more of the aforementioned clinical features.

2.2. Clinical analysis

Extracted clinical data included patient's age at the time of rhabdomyolysis, clinical symptoms prior to the rhabdomyolysis, precipitating factors, number of episodes and related complications of rhabdomyolysis, and pattern of muscle weakness. The muscle strength was graded as normal (MRC = 5), mildly (MRC = 4), moderately (MRC = 3–4) or severely reduced (MRC < 3). Reviewed laboratory data included results of electromyographic (EMG), serological, muscle histochemical, immunocytochemical and biochemical studies, and of molecular studies confirming the diagnosis of a muscular dystrophy.

We reviewed separately similar data from patients who experienced one or more episodes of rhabdomyolysis prior to developing significant muscle weakness, in whom muscular dystrophy was clinically suspected but such diagnosis could not be confirmed by either muscle immunohistochemical analysis or limited molecular testing. These patients had fixed muscle weakness, persistently elevated CK values and EMG or histopathologic evidence of a chronic myopathy. All patients had negative serum and urine metabolic markers, preserved myophosphorylase reactivity on muscle biopsy and normal muscle biochemical assay of commercially available glycolytic enzymes (phosphorylase, phosphorylase b kinase, phosphofructokinase, phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase), myoadenylate deaminase and CPT2.

3. Results

3.1. Patients with genetically confirmed diagnosis of a muscular dystrophy and rhabdomyolysis

Pertinent clinical and laboratory features of these patients are summarized in Tables 1 and 2. Thirteen unrelated patients, 6 males and 7 females, were identified (patients 1 and 3 were previously reported [13, 18]). The median age was 18 years (range, 2–47 years) at the time of the first episode of rhabdomyolysis and 23 years (range, 2–53 years) at the time of our clinical evaluation. Four patients reported recurrent rhabdomyolysis.

Exercise was the most common precipitant (n = 6), followed by febrile illness (n = 4). Rhabdomyolysis had no identifiable trigger in 3 patients. No patient was on lipid-lowering medications. One or more episodes of rhabdomyolysis were severe enough to require hospitalization in all but one patient. CK measurements at the time of rhabdomyolysis were available in 9 of the 13 patients and ranged between 12,000 and 186,000 IU/L. Laboratory data pertinent to the episode of rhabdomyolysis were not available for the other 4 patients, who also manifested urine discoloration, severe myalgia, muscle weakness and CK elevation (reportedly above 10,000 IU/L) requiring hospitalization (hospitalized at another institution). As result of the rhabdomyolysis, one of these 4 patients developed anterior compartment syndrome requiring fasciotomy in both legs (patient 4) and another (patient 9) had acute renal failure that resolved spontaneously.

Eight of the 13 patients were asymptomatic prior to the rhabdomyolysis; 3 had experienced myalgias or exercise intolerance for a variable length of time (range, 1–30 years), and 2 slowly progressive mild muscle weakness for which they had sought no medical attention until development of the rhabdomyolysis. Seven patients had prior exposure to general anesthesia with no complications. Neurologic examination, performed outside an episode of rhabdomyolysis (years after the rhabdomyolysis for patients 6 and 7), revealed normal muscle strength in 3 patients, mild to moderate proximal weakness in 10 patients. Calf muscle enlargement was present in 6 patients. The baseline CK values ranged from 600 to 3,600 IU/L (median, 1200 IU/L). Needle EMG study was available in 8 adult patients and showed myopathic changes in proximal muscles in 7, associated fibrillation potentials in 2, and normal findings in one. Muscle biopsy, performed in 11 patients, revealed chronic myopathic changes (fiber size variation, muscle fiber necrosis or regeneration and increased endomysial and perimysial fibrous connective tissue) in 8, interstitial congophilic deposits in 2 of the 3 anoctaminopathy-5 patients, and normal histological findings in 2 patients. Thirteen patients underwent cardiac evaluation by ECG and echocardiogram, which demonstrated evidence for hypertrophic cardiomyopathy in one calpainopathy-3 patient and left ventricular hypertrophy in one dystrophinopathy patient.

A definite molecular diagnosis was available in all 13 patients. Limb-girdle muscular dystrophy 2I (LGMD2I) due to mutations in *FKRP* (n = 6) was most frequent underlying muscular dystrophy, followed by anoctaminopathy-5 (n = 3), calpainopathy-3 (n = 2) and Duchenne muscular dystrophy (n = 2). Alpha-dystroglycan (α-DG) immunoreactivity was reduced only in 3 of the 4 patients with *FKRP* mutations in whom immunocytochemical studies were performed. (illustrative Fig. 1) The median length of time between the first episode of rhabdomyolysis and the molecular diagnosis of muscular dystrophy was 2 years (range, 1 month to 23 years). The 2 youngest patients (patients 6 and 7) presenting with rhabdomyolysis had Duchenne muscular dystrophy. Although no obvious muscle weakness was elicited at the time of their diagnosis (only calf muscle enlargement), their clinical phenotype was compatible with Duchenne muscular dystrophy at the time of last clinical evaluation at age 7 and 8 years, respectively. Five patients were previously misdiagnosed with metabolic myopathy (n = 3), inflammatory myopathy (n = 1) or viral myositis (n = 1).

Thirteen additional patients (age range, 5 to 56 years) with clinically and pathologically suspected muscular dystrophy of unknown molecular defect had history of recurrent rhabdomyolysis, which was unprovoked, exercise or fever induced. Due to the lack of the genetic diagnosis, these patients were excluded from the study.