The role of muscle biopsy in the diagnostic process of rhabdomyolysis: large retrospective study and proposal of a revised diagnostic workflow

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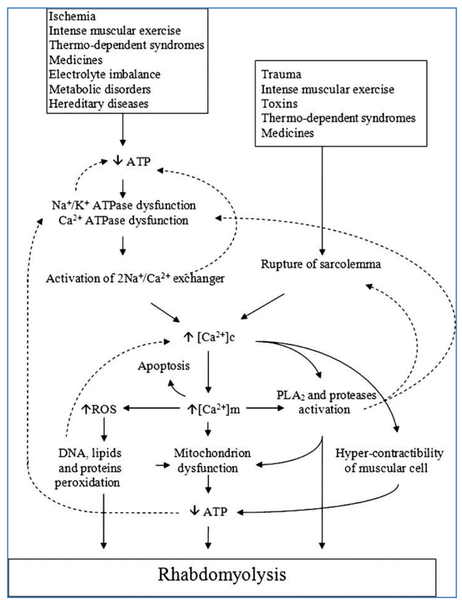
Introduction

Rhabdomyolysis is an acute, and frequently severe, pathological event characterized by rapid necrosis of striated muscle tissue. Both acquired (crush syndrome, numerous toxic, disendocrine diseases, intense exercise) and genetic (disorders of glucose or lipid metabolism, mitochondrial diseases, muscular dystrophies, calcium-related disorders) causes can lead to this dramatic event. The identification of the etiological cause can be extremely complex, long, and costly, and frequently no definitive diagnoses can be acquired.

Aim of the study was to evaluate the role of muscle biopsy in the diagnostic process of rhabdomyolysis.

Fig. 1. Mechanisms of rhabdomyolysis



Matherial and Methods

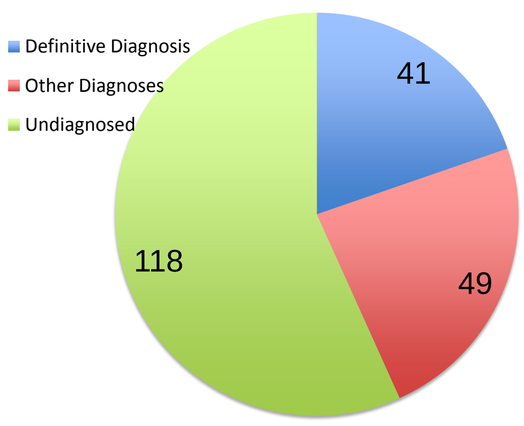
We analysed the clinical features and diagnostic process in a large retrospective study including all patients that were referred for rhabdomyolysis between 2000 and 2016, in which an external cause of rhabdomyolysis was excluded.
All clinical data concerning the episode and the intercritical period were collected, as well as the results of all diagnostic tools performed.

N	208
Sex	152M; 56F (ratio 2.69)
Age at first visit	34,2±12,9
Pts w/ single episode	109 (52,2%)
Pts w/several episodes	99 (47,8%)

Table I. Patient cohort

Results

Fig. 2. Final diagnoses



A) DEFINITIVE DIAGNOSIS
(= genetic / enzymatic / histopathological diagnosis acquired)

1. CPT2 n = 11
2. McArdie disease n = 11
3. RYR1 myopathy n = 8
4. VLCAD n = 2
5. BMD n = 2
6. PGM1 n = 2
7. Other (DM2, DM1, FKRP, LIPIN1, DNA2) n = 5

B) OTHER DIAGNOSES (= clinical diagnosis)

1. Exertional r. n = 37
2. Drug-induced n = 3
3. Infectious disease n = 3
4. Toxic n = 2
5. Inflammatory m. n = 2
6. Basedow n = 1
7. Popliteal Artery Entrapment Syndrome n = 1

Fig. 3. Histopathological features of muscle biopsies of patients presenting rhabdomyolysis

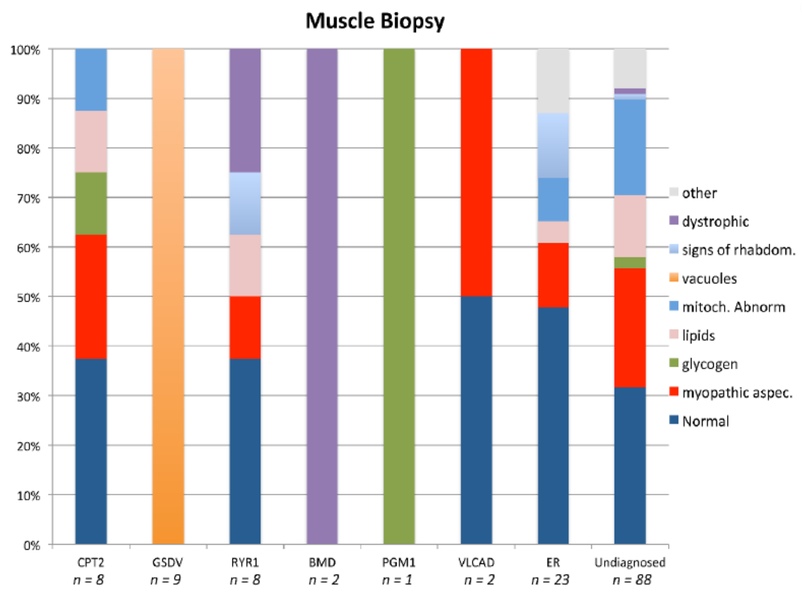


Fig. 4. Age at first episode and max CK levels of patients with different disease. Patients with CPT2, BMD and VLCAD invariably presented firs episode <20 years of age; RYR1 and CPT2 can reach higher CK leves during episodes.

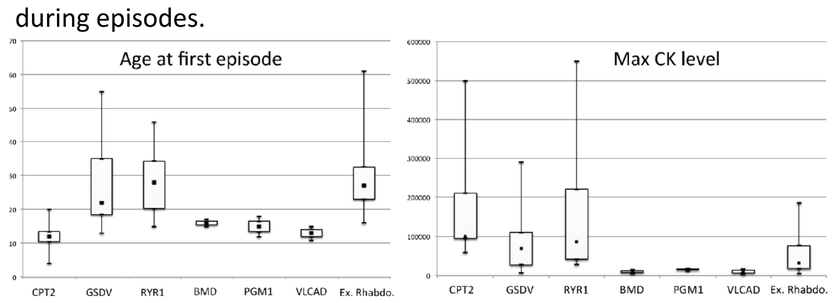
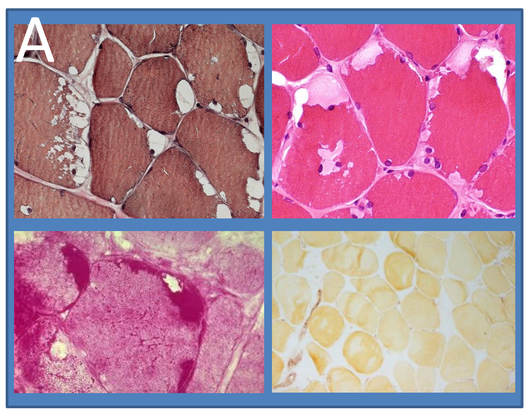
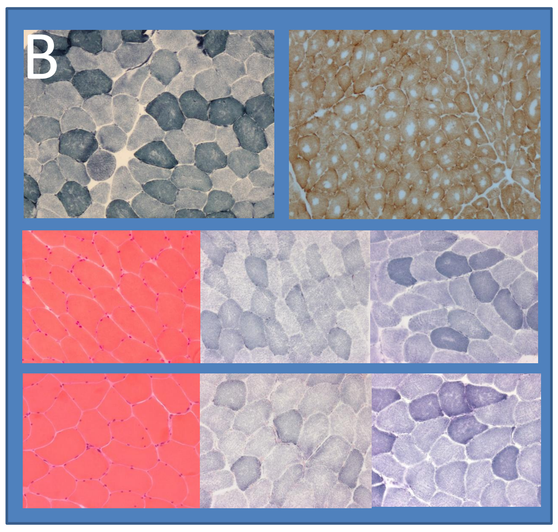
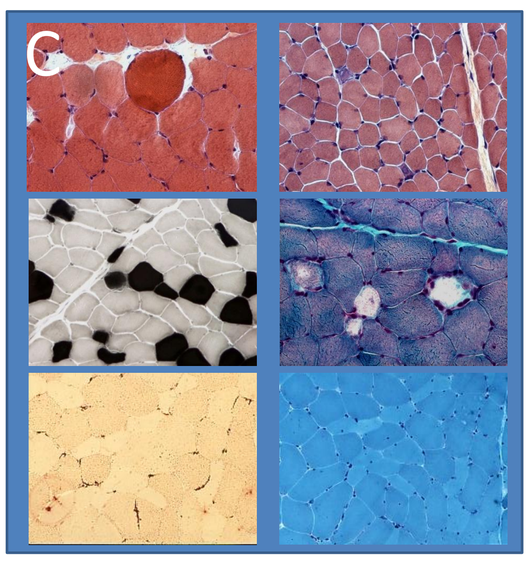
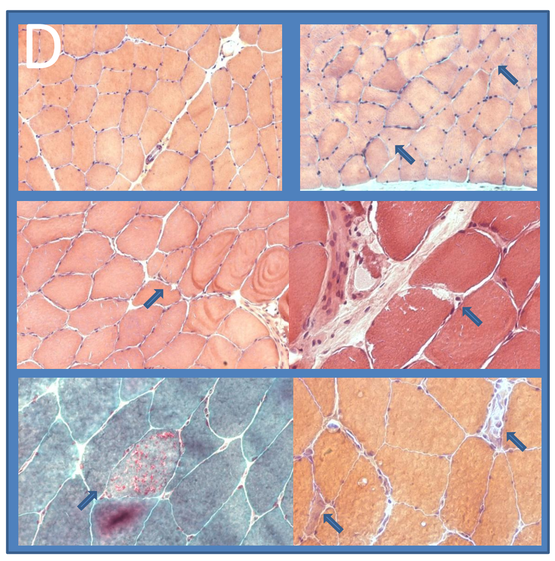


Fig.5 Histopathological features of McArdle disease (A), RYR1 myopathy (B), CPT2 deficiency(C), undiagnosed rhabdomyolysis (D)







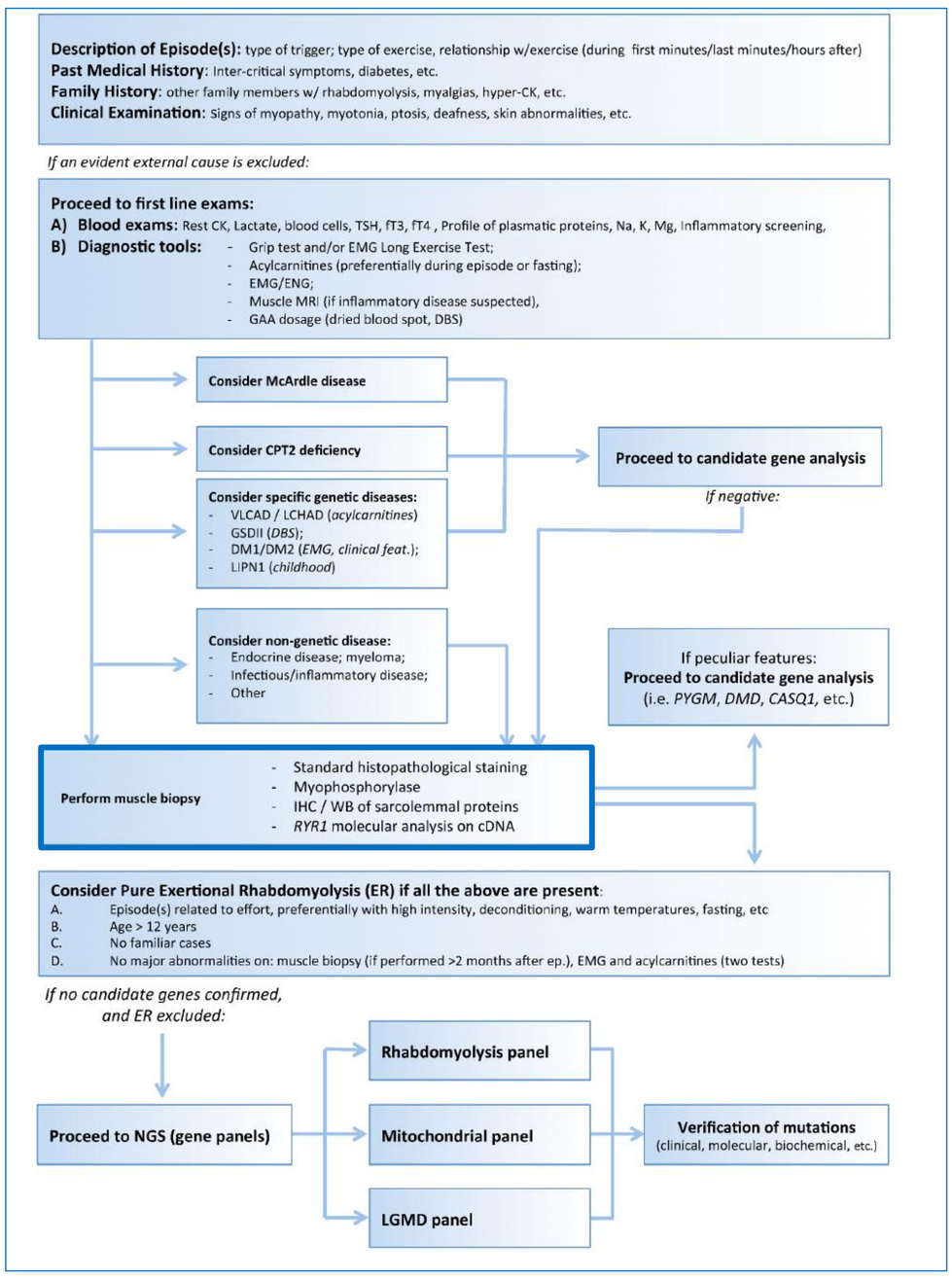


The clinical features of the episodes, the inter-critical clinical characteristics and laboratory results could guide toward specific molecular diagnoses only in few cases.

1. **GSDV** is the easiest diagnosis, because of the typical clinical features and the unique results of diagnostic work up (handgrip test, muscle biopsy).
2. **CPT2** need to be suspected when the trigger is a long effort, or fasting, or fever. Acylcarnitines can be evocative. It is one of the most frequent cause of rhabdomyolysis
3. **VLCAD** can be suspected when the profile of acylcarnitines is supportive of the diagnosis (if normal it should be repeated during episodes or after 8h fasting).

Other diagnostic tools were less useful, or more expensive and time consuming:

- EMG: 19 aspecific myopathic changes/109 tests
- CPT2 dosage on white blood cells: 8 reduction/87 tests
- Dosage of mitochondrial respiratory chain activity : 8 aspecific reduction /20 tests
- Study of glyco(geno)lysis enzyme on muscle biopsy or blood cells: 2 specific reductions, 2 global reductions, 14 normal tests
- Halothane and caffeine in vitro muscle contracture tests: 1 /4 abnormal tests
- Single gene analysis: 37 genetic diagnoses / 102 genes studied



Conclusions

The diagnostic protocol for rhabdomyolysis is still inefficient. Muscle biopsy has an important role, but histopathological picture can be variable and misleading. We suggest a new diagnostic algorithm for rhabdomyolysis, in which clinical features and few first-line tests exclude the most frequent causes or the treatable ones. The subsequent muscle biopsy identifies certain myopathies and guide toward the use of specific genetic panels (Next Generation Sequencing) for metabolic myopathies, muscular dystrophies or mitochondrial diseases. This diagnostic algorithm will allow cost reduction and time optimization, and hopefully will increase the rate of etiological diagnosis of rhabdomyolysis.

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