HOW TO APPROACH HYPERCKEMIA (AND RHABDOMYOLYSIS)

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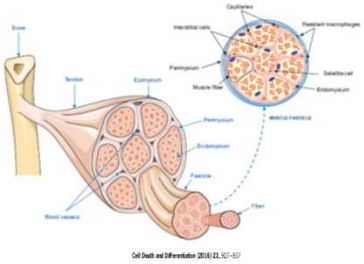
PHYSIOLOGY OF SKELETAL MUSCLE



PHYSIOLOGY OF MUSCLE ENZYME

- Creatine kinase
- Aldolase
- Lactate dehydrogenase
- Aminotransferases

CREATINE KINASE

- The most widely used enzyme to diagnose and follow muscle disease.
- It is present in the highest concentrations in serum in response to muscle injury, is the most sensitive indicator of muscle injury
- The best measure of the course of muscle injury

More details to follow

WHAT IS CREATININE (PHOSPHO) KINASE ?

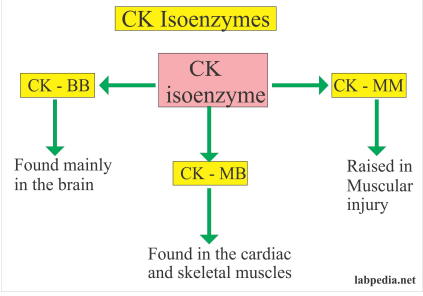
CK: a roughly 86-kilodalton dimeric enzyme whose function is to catalyze the combination of creatine and adenosine triphosphate (ATP) to form phosphocreatine and adenosine diphosphate (ADP),

a reaction crucial for cellular energy generation and metabolism.

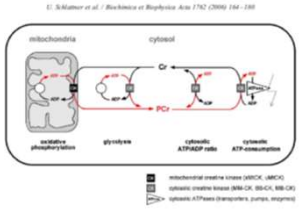
There are 3 isoenzymes,

- CK-MM (predominantly present in skeletal muscle),
- CK-MB (present in cardiac muscle)
- CK-BB (present in brain).

When measured, the total serum CK level reflects the sum of all 3 isoenzymes



THE CREATINE KINASE/PHOSPHOCREATINE SYSTEM



ALDOLASE

- Aldolase is another glycolytic pathway enzyme that is found in all tissues but predominantly in skeletal muscle, liver, and brain.
- While increased aldolase levels are not as specific or sensitive for muscle disease as CK levels, aldolase concentrations are occasionally elevated in patients with myositis who have normal CK levels

LACTATE DEHYDROGENASE

- Lactate dehydrogenase (LDH) catalyzes the final step of glycolysis, converting pyruvate to lactate .
- It is found in nearly every tissue of the body; as a result, increased serum levels are found in a great variety of disease states.

AMINOTRANSFERASES (AST, ALT)

- The aminotransferases (transaminases) catalyze the conversion of the amino acids alanine (ALT) and aspartate (AST) to alpha-ketoglutarate, providing a source of nitrogen for the urea cycle
- Both enzymes are found widely in many tissues, and increased serum levels are a nonspecific indicator of disease.
- Serum concentrations are highest in various hepatic disorders, but increased values are also seen in skeletal muscle, myocardial disease, and hemolysis.

MUSCLE ENZYME SUMMARY

- Serum aldolase concentrations are occasionally elevated in patients with myositis who have normal CK levels, but increased aldolase levels are not as specific or sensitive for muscle disease as CK levels.
- LDH and the aminotransferases are present in many tissues and are often elevated with skeletal muscle injury.

Neuromuscular causes of elevated muscle enzymes

Inflammatory myopathy	**Drugs**
Dermatomyositis and polymyositis	Colchicine
Juvenile dermatomyositis and polymyositis	Antimalarials
Myositis with associated connective tissue disease: Sjögren's syndrome, scleroderma, lupus, rheumatoid arthritis	Penicillamine
Localized myositis	Zidovudine
Inclusion body myositis	Lipid-lowering agents: statins, fibrates, niacin
Systemic necrotizing vasculitis	Alcohol
Polymyositis associated with graft-versus-host disease	Cocaine
Behçet's disease	Nondepolarizing muscle relaxants with high-dose corticosteroids
Sarcoidosis	**Metabolic myopathies**
Infectious myopathy	Carbohydrate metabolism enzyme deficiencies
Bacterial pyomyositis	Lipid metabolism enzyme deficiencies
Viral myositis	Purine metabolism enzyme deficiencies
Mycobacterial myositis	**Malignant hyperthermia**
Fungal myositis	**Endocrine myopathies**
Parasitic myositis	Hypothyroidism
Spirochetal myositis	Acromegaly
Dystrophinopathies	**Periodic paralyses**
Duchenne	Familial periodic paralysis
Becker	Thyrotoxic periodic paralysis
Fascio-scapulo-humeral	**Post-exercise**
Limb-girdle	**Iatrogenic**
Myotonic dystrophy	Intra-muscular injection
Duchenne and Becker carriers	Electromyography
Rhabdomyolysis	Intraoperative muscle injury
Trauma, crush injuries, coma	**Motor neuron disease**
Extreme exertion	Amyotrophic lateral sclerosis
Environmental heat illness	Spinal muscular atrophies
Seizures, delerium tremens	
Electrolyte disturbances: hypokalemia, hypophosphatemia	

ELEVATED MUSCLE ENZYMES IN THE ABSENCE OF MUSCLE DISEASE

- Exercise
- Iatrogenic muscle injury
- Motor neuron disease
- Asymptomatic elevation (HyperCKemia)

EXERCISE

Peak level at 8-24 hours after exercise ,

Begin to decrease at 24 to 48 hours, and return to baseline levels by 72 hours

The increase in CK levels is related to the intensity and duration of exercise and is greater in untrained than trained individuals

Serum lactate dehydrogenase (LDH) and transaminase levels follow a similar pattern after exercise, although the increase is not as great as with CK

IATROGENIC MUSCLE INJURY

Follow the same temporal pattern after an IM injection, major surgery, electromyography (EMG), or muscle biopsy.

The muscle enzyme elevations in the last two settings may confuse serum muscle enzyme measurements in the evaluation of myopathy

Major surgical procedures, particularly orthopedic and spinal surgery, cause serum enzyme elevation due to direct muscle trauma and to ischemic compression of muscle due to positioning during the procedure

MOTOR NEURON DISEASE

Mild elevations in 75 percent of ALS cases, particularly in the early phases of the disease and more commonly in men

The highest measured CK concentration was 11 times normal, and the mean CK for the entire group was about two fold greater than normal,

- possibly leading to misdiagnosis of an inflammatory myopathy or inclusion body myositis.

Mild elevation < 2 times in SMA

ASYMPTOMATIC ELEVATIONS IN CREATINE KINASE

- Individuals with persistently elevated CK but with no or minimal muscle symptoms and no weakness present a diagnostic dilemma.
- Persistent elevation of CK in the absence of an underlying disease process or explanation has been termed hyperCKemia
- Muscle biopsies in these individuals are infrequently diagnostic
  - In those patients in whom a specific diagnosis can be made, it is usually a disorder for which there is no treatment, such as a dystrophy or a metabolic myopathy with a benign outcome.

WHAT IS NORMAL CK?

Three groups of CK

(1) a "high CK" group : black men,
with mean CK level was 237.8 ± 492.1 U/L

(2) an "intermediate CK" group consisting of non-black men and black women
with mean CK levels ranging between 109.3 and 149.7 U/L;

(3) a "low CK" group of white women
with mean CK levels ranging between 64.6 and 79.8 U/L.

Wong ET, et al.. Am J Clin Pathol 1983;79:582– 586.

WHAT IS NORMAL CK?

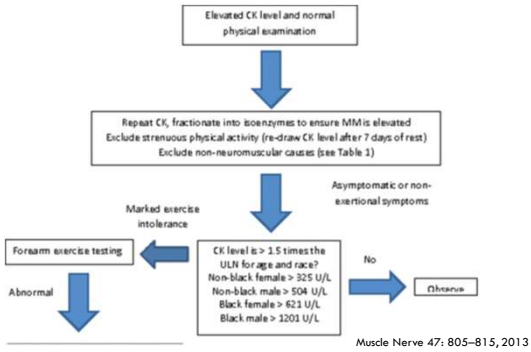
The reasons for these differences are not entirely clear, may be related to

- differences in skeletal muscle mass,
- total body mass
- inherited differences between races in the permeability of the sarcolemma to CK

Wong ET, et al.. Am J Clin Pathol 1983;79:582– 586.

WHAT IS HYPERCKEMIA ?

- Normal level of CK: varied from lab to lab
- EFNS guideline (2010): at least 1.5 times upper normal limit



Muscle Nerve 47: 805–815, 2013

Table 1. Systemic causes of hyperCKemia.

Endocrine disorders	Toxins
Hyperthyroidism	Ethanol
Hypothyroidism	Cocaine
Hypoparathyroidism	Heroin
Connective tissue disorders	Metabolic disturbances
Cardiac disease	Hyponatremia
Acute kidney disease	Hypokalemia
Viral illnesses	Hypophosphatemia
Pregnancy	Strenuous exercise
Celiac disease	Muscle trauma
Medications	Intramuscular injections
HMG-CoA reductase inhibitors (statins)	Needle electromyography
Fibrates	Seizures
Anti-retrovirals	Surgery
Beta-blockers	Malignancy
Clozapine	MacroCK
Angiotensin receptor blocking agents	
Hydroxychloroquine	
Isotretinoin	

MYOGLOBINURIA AND RHABDOMYOLYSIS

Definition & General features

- Acute syndrome due to extensive injury of skeletal muscle
- Muscle fiber pathology
  - Necrosis or permeabilization of sarcolemma
  - Release of muscle proteins into circulation
- Serum CK: > 10,000, Usually > 30,000
- Most common causes: Exercise, Drugs & Alcohol

More likely hereditary etiology

Clinical patterns: Distinctive features

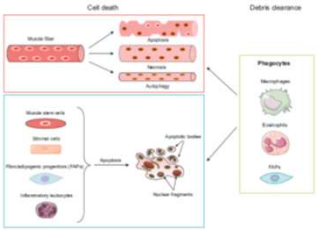
- Rhabdomyolysis on minimal exertion or fasting
- Family history
- Multiple episodes

MECHANISMS OF MUSCLE INJURY

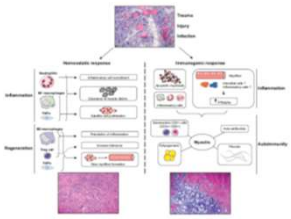
Rise in free intracellular calcium: Due to
- Damage to muscle sarcolemma
- Failure of energy supply within muscle cell

Activation of calcium-dependent neutral proteases & phospholipases
- Destroys myofibrillar, cytoskeletal, and membrane proteins
- Lysosomal digestion of muscle fiber contents ensues

CELL DEATH AND PHAGOCYTIC CLEARANCE IN SKELETAL MUSCLE.



ADAPTIVE AND MALADAPTIVE MUSCLE REMODELING



TYPICAL CLINICAL FEATURES

Muscle
- Weakness: Proximal > Distal
- Discomfort: Pain; Tenderness
- Swelling
- May be asymptomatic

Renal:
- More severe cases
- Dysfunction
- Urine: Pigmenturia; "Tea-colored"

General
- Fever
- Leukocytosis
- Cardiomyopathy
- Encephalopathy

COMMON CAUSES

Adults: Non-recurrent myoglobinuria
- Alcohol & Drug abuse
- Muscle Compression or Trauma
  - Acute
  - Falls
  - Prolonged immobility
- Seizures
- Multiple contributing factors

Children: Non-recurrent myoglobinuria

Infections: Common cause in children
- Viral: Myositis (Influenza B); Influenza; CMV; EBV; Group A beta hemolytic streptococci
- HIV: Acute retroviral syndrome
- Bacterial: Legionella; Salmonella
- Malaria

Trauma

Nonketotic hyperosmolar coma

Dystonia

Malignant hyperthermia

Recurrent myoglobinuria: Metabolic & Hereditary disorders

Most common
- 1st decade: Lipin-1
- Myophosphorylase
- CPT II
- Idiopathic

PREDISPOSING & PRECIPITATING FACTORS

Exercise: Progressive exercise produces fatigue & myalgia

Fasting

Hypokalemia

High ambient temperatures

Infections

Increased age: Falls

Toxins & Drugs

Genetic

TIME COURSE

Early: Pigment in urine may occur immediately or with delay up to 24 hours

Late: Severe rhabdomyolysis may be followed by fibrosis & contractures

COMPLICATIONS

Renal failure with acute tubular necrosis: Due to
- Ferrihemate toxicity: Dissociates from globulin below pH 5.6
- Tubular obstruction: Precipitation of myoglobin casts
- Alterations in glomerular filtration rate
- Myoglobin toxicity: Treatment is Volume expansion
  - Mannitol or Normal saline: Maintain urine output at 200 to 300 ml/hr
- Hypotension
- Crystal formation: Alkalinize urine with Na bicarbonate
- Protease release from muscle: Avoid nephrotoxic agent

Hyperkalemia
- Due to: Muscle breakdown; Renal failure
- Treatment: Calcium gluconate; Diuresis

Hypocalcemia: Due to binding by damaged muscle & hyperphosphatemia

Hypercalcemia
- Due to: Release from muscle; Reduced renal excretion
- Treatment: Diuresis

Compartment syndrome
- Muscles in closed space swell & become ischemic
- May require fasciotomy

Hyperphosphatemia & Tissue calcification
- Due to: Release of organic & inorganic phosphates from muscle
- Treatment: Diuresis

Disseminated intravascular coagulopathy

LABORATORY

Urine dip stick (benzidine)
- Positive: Myoglobin; Hemoglobin; Hematuria
- Negative: Porphyria

Myoglobin
- Urine
  - Precedes rise in CK
  - Visible pigmentation with level > 1 g/L
  - Testing: Radioimmunoassay; Use urine fresh & neutralized
  - Urinalysis pattern: Albumin & Heme with Few RBCs

Serum
- Normal levels: 3 to 80 µg/L
- Rhabdomyolysis: High

Serum CK
- Very high: > 20,000; Up to hundreds of thousands
- Half life: 1 to 3 days

Serum lactate
- Glycogenoses: No rise with exercise
- Mitochondrial disorders: Rise with minimal exercise

Serum carnitine: Low in β-oxidation disorders, especially during attack

Acylcarnitine profile

MRI with gadolinium enhancement: Increased signal; $T_2 > T_1$

MUSCLE BIOPSY

Useful for diagnosis in some hereditary disorders

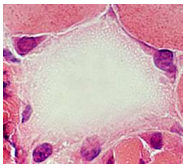
Pathology: Scattered muscle fiber necrosis & degeneration

Metabolic analysis: Perform at least 1 month after episode
- Biopsies performed near time of rhabdomyolysis will give spurious biochemical results

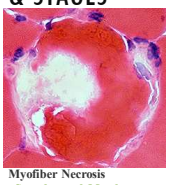
Suggestive changes
- Lipid storage
- Aldolase A
- ACADVL
- ETFDH
- Tubular aggregates: PGAM2

Cores: RYR1
Chronic myopathy
- ANO5
- Dysferlin
- Dystrophin
- FKTN
- FKRP

NECROSIS: GENERAL FEATURES & STAGES

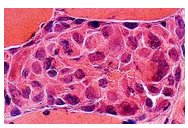


Myofiber Necrosis
Metabolic
Early stage
Muscle Fiber cytoplasm: Pale
Myonuclei: Lose staining

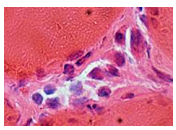


Myofiber Necrosis
Sarcolemmal Membrane
Early stage
Muscle Fiber Cytoplasm
"C" or Δ Lesion
Regional Hypercontraction

NECROSIS: GENERAL FEATURES & STAGES

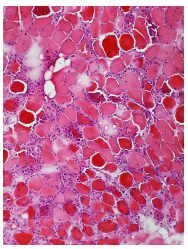


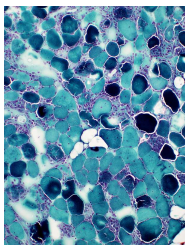
Myofiber Necrosis
Phagocytic
Later stage
Muscle Fiber:
Replaced by macrophages.



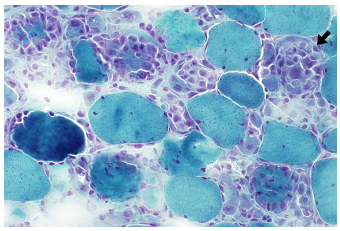
Myofiber Necrosis
Collapse
Very Late stage
Muscle Fiber: Collapse
Macrophages have migrated away

SEGMENTAL NECROSIS: SCATTERED NECROTIC & HYPERCONTRACTED MUSCLE FIBERS

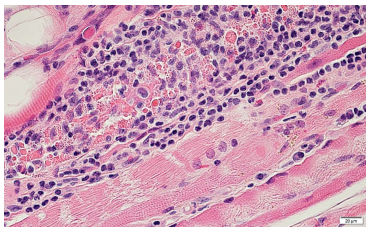




NECROTIC MUSCLE FIBERS: PHAGOCYTOSIS (ARROWS)



NECROTIC MUSCLE FIBER LARGELY REPLACED BY CELLS, SOME REMAINING DEBRIS



TREATMENT

- Maintain airway & circulation
- Prevent acute tubular necrosis
  - Normal saline IV: 10 to 15 mL/kg; Continue if adequate urine output
  - Isotonic Sodium bicarbonate
  - Mannitol: 0.3 to .05 g/kg IV; Monitor K^+
  - Furosemide: 40 to 80 mg IV initially; Up to 200 mg total
- Treat other complications
  - Hyperkalemia
  - Disseminated intravascular coagulation
- Treat specific underlying condition: Diet; Ribose; Riboflavin; Carnitine

CREATINE KINASE (CK): UNEXPECTEDLY HIGH

High CK with few, no, or atypical symptoms: Causes

- Endocrine
  - Hypothyroid
  - Hypoparathyroid
- Exercise: Acute & Producing Muscle Hypertrophy
- Muscle Trauma: Injections (esp phenothiazines); Psychosis; Falls

SPECIAL SITUATION

CREATINE KINASE (CK): UNEXPECTEDLY HIGH

CK time course after injury

- Onset of rise: < 12 hours
- Peak values: 1 to 3 days
- Decline: 3 to 5 days
- Half life: 36 to 48 hours

Failure to decrease: Ongoing muscle injury

EMG as a cause of high CK

- Rarely elevates a normal CK to abnormal levels
- Peak CK: 1x to 1.5x baseline in 6 hours
- Return to baseline: 48 hours

Myopathies (asymptomatic)Dystrophy
- Dystrophinopathy
- Limb-Girdle MD (LGMD): 1C; 2A; 2B; 2P

Metabolic
- Glycogen Storage Disorders
- CPT2 deficiency
- AMPDA deficiency

Other hereditary myopathy
- Central core
- Danon
- Distal
- Malignant Hyperthermia
- Mitochondrial disease
- Myofibrillar myopathy
- Myopathy with tubular aggregates
- Myotonia: Congenita; DM2
- Rippling muscle syndromes

Acquired disorders
- Inflammatory
- Drug toxicity

Denervation
- Motor neuron diseases
- Small fiber polyneuropathies
- Not: Sensory-Motor polyneuropathies

Idiopathic
- Hereditary Idiopathic
- Other Idiopathic: 50% to 80% of HyperCKemia
- Normal muscle: 30%
- Non-specific muscle abnormalities: 30%

CREATINE KINASE (CK): LOW

Muscle disease
- Reduced muscle mass: End-stage disease
- Corticosteroid treatment
- Myosin-loss: Especially weeks after onset
- Dermatomyositis, childhood type: Some patients

Hyperthyroidism

Multiorgan failure

Rheumatic diseases: Active inflammation
- Rheumatoid arthritis
- Systemic lupus erythematosis
- Spondyloarthropathies
- Fasciitis
- Perimysitis

Clin Rheumatol 2000;19:296-300

ASYMPTOMATIC HYPERCKEMIA

Table 4. HyperCKemia literature: abnormal EMG by study.

Study	Abnormal EMGs/total EMGs performed
Brewster et al.[69]	4/14 (28.6%)
Dabby et al.[43]	8/27 (28.9%)
Fernandez et al.[52]	23/57 (40.4%)
Joy and Oh[66]	14/19 (73.7%)
Malandrini et al.[70]	15/37 (40.5%)
Prelle et al.[60]	57/100 (57%)
Reijneveld et al.[76]	9/30 (30%)
Simmons et al.[67]	9/20 (45%)
Total	139/304 (45.7%)

MUSCLE & NERVE June 2013

Table 3. HyperCKemia literature: abnormal muscle biopsy by study.

Study	Abnormal biopsies/total number of biopsies performed	Diagnostic biopsies/ total number of biopsies performed
Brewster et al.[69]	4/14 (28.6%)	0/14 (0%)
Dabby et al.[43]	22/40 (55%)	3/40 (7.5%)
Fernandez et al.[52]	83/104 (79.8%)	51/104 (49%)
Joy and Oh[56]	15/19 (78.9%)	15/19 (78.9%)
Malandrini et al.[70]	34/37 (91.9%)	3/37 (8.1%)
Prelle et al.[60]	44/114 (38.6%)	20/114 (17.5%)
Reijneveld et al.[76]	24/31 (77.4%)	0/31 (0%)
Simmons et al.[68]	11/20 (55%)	6/20 (30%)
Filosto et al.[67]	83/105 (79%)	15/105 (14.3%)
Total	320/484 (66.1%)	113/484 (23.3%)

'Biopsies with "mild, nonspecific myopathic findings" reflect the difference between the number of abnormal muscle biopsies and those that were diagnostic.

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Table 5. HyperCKemia literature: overall likelihood of making a definitive diagnosis by study.

Study	Number of patients diagnosed/ total number of patients
Brewster et al.[69]	10/14 (71.4%)
Dabby et al.[43]	3/40 (7.5%)
D'Adda et al.[75]	6/55 (10.9%)
Fernandez et al.[52]	57/104 (54.8%)
Joy and Oh[56]	15/19 (78.9%)
Lilleng et al.[74]	4/97 (4.1%)
Malandrini et al.[70]	3/37 (8.1%)
Prelle et al.[60]	21/114 (18.4%)
Simmons et al.[67]	6/20 (30%)
Total	125/445 (28.1%)

CONCLUSION

Still, muscle biopsy offers the best chance of pinning down an etiology.

Even with diagnostic biopsies, however, the chances of finding a treatable disorder are very low.

As our understanding of inherited myopathies and metabolic disorders grows over time, it is likely that more patients with otherwise idiopathic hyperCKemia will be found to harbor occult, albeit mild, neuromuscular disorders.

EFNS GUIDELINES ON THE DIAGNOSTIC APPROACH TO PAUCI- OR ASYMPTOMATIC HYPERCKEMIA

1. HyperCKemia is defined as sCK >1.5 times the ULN
   (see revised values in Table 2).

2. Consider all non-neuromuscular causes in Tables 3 and 4 and other non-myopathic causes of hyperCKemia that might explain their high sCK.

3. Enquire about any family history of neuromuscular disease, hyperCKemia or malignant hyperthermia

European Journal of Neurology 2010, 17: 767–773

Table 1 97.5th percentile for serum creatine kinase (CK) activity (iu/l). Derived from Brewster *et al.* 2007

	Non-black Female	Non-black Male	Black Female	Black Male
CK iu/l	217	336	414	801

Table 2 Percentage of normal individuals with creatine kinase activity above the upper limit of normal (ULN) (Personal communication Brewster *et al.* 2007)

	Non-black Female	Non-black Male	Black Female	Black Male
1.0 ULN	2.5	2.5	2.5	2.5
1.5 ULN	1.5 (325)	1.0 (504)	1.3 (621)	0.5 (1201)
2.0 ULN	0.2	0.8	0.5	0

The value in bracket represents 1.5× ULN

European Journal of Neurology 2010, 17: 767–773

Table 3 Causes of hyperCKemia unrelated to a recognized neuromuscular disease

Medications
Strenuous muscle exercise (especially eccentric)
Trauma (electromyogram studies, IM injections)
Surgery
Toxins (alcohol, heroin, cocaine)
Endocrine (hypothyroidism, hypoparathyroidism)
Viral illness
Metabolic (hypokalaemia, hyponatraemia)
'Idiopathic' (sporadic and familial)
Race (black > non-black)
Sex (male > female)
Chronic cardiac disease (CK-MB)
Obstructive sleep apnoea
Neuroacanthocytosis syndromes
Macro-CK
Malignant hyperthermia syndrome

4. Before embarking on long and expensive investigations, it is advised that hyperCKemia is confirmed by repeat assay and that the possibility of normal exercise induced elevation is excluded.

Therefore, the patient should be advised to avoid strenuous exercise for 7 days prior to sampling and at least two samples 1 month apart should be taken.

5. If hyperCKemia is confirmed to perform a nerve conduction study and EMG.

6. A biopsy may be performed in a patient with hyperCKemia if one or more applies:

(i) If the EMG is abnormal (myopathic)

(ii) If sCK is ‡3 times normal.

(iii) If the age of the patient is <25 years.

(iv) Exercised-induced pain or exercise intolerance.

(v) Women with hyperCKemia but sCK<3 times normal (because of the possibility of Duchenne/ Becker mutation carrier status).

However, prior to biopsy, DNA analysis on blood lymphocytes should be undertaken. Currently, multiple ligation probe amplification analysis will identify 70% of carriers.

Developing technology is probably to improve that and all such cases should be discussed with local genetic services.

Table 5 Genetic myopathies that can present as isolated hyperCKemia

	References
Adult onset glycogenosis type II	[12]
Caveolinopathy (Caveolin-3)	[17–19]
Calpainopathy (Calpain-3)	[20,21]
Desminopathy	[22,23]
Dysferlinopathy (LGMD and Miyoshi)	[9,21,24,25]
Fukutin-related protein (FKRP) LGMD 2I	[25]
Dystrophinopathy (also female carriers)	[26–29]
Sarcoglycanopathy	[30]
Myotonic dystrophy type 2	[31]

Table 6 Diagnoses in patients with pauci- or asymptomatic hyperCKemia

Diagnoses	Joy *et al.*, 1989	Reijneveld *et al.*, 2001	Prelle *et al.*, 2002	Simmons *et al.*, 2003	Fernandez *et al.*, 2006	Dabby *et al.*, 2006	Filosto *et al.*, 2007	Malan-drini *et al.* 2008	Total
Specific myopathies	12/19	6/37	21/114	6/20	55/104	3/40	15/105	3/37	121/460
Muscular dystrophies									25
Dystrophinopathy		2	5		9	3		1	17
Dysferlinopathy			1		1				2
Caveolinopathy					1				1
Calpainopathy					1				1
Sarcoglycanopathy		1							1
LGMD-unspecified			1						1
Fukutin-related protein					2				2
Metabolic myopathies									50
CPT 2 def.			4	2					6
Myophosphorylase	1	1			15				17
Phosphofructokinase def.							1		1
1 α, glucosidase def.					9		5		14
Glycogenoses (unspecified)					1				1
Phosphorylase-b kinase				3					3
Adenylate deaminase			1	1					2
Mitochondrial	2		2		1		1		6

Inflammatory myopathy									20
Polymyositis	5				6			1	12
Inclusion body myositis	1				2				3
Macrophagic myositis					5				5
Congenital myopathy									8
Central core	1	1	1				2	1	6
Centronuclear							1		1
Multicore	1								1
Miscellaneous									14
Malignant hyperthermia myopathy			3						3
Tubular aggregates		1	1				3		5
Myofibrillar myopathy					2				2
Lobulated fibre myopathy							2		2
Desminopathy			1						1
Sarcoid myopathy	1								1
Myotonia fluctuans			1						
Non-specific myopathic	3/19	24/37	18/114	3/20	26/104	19/40	68/105	29/37	190/460
Neurogenic			13/114		2/104		8/105	2/37	25/460
Normal	4/19	7/37	62/114	11/20	15/104	18/40	14/105	3/37	134/460

7. Men with hyperCKemia and a sCK<3 times normal may be offered a biopsy if they are seriously concerned about neuromuscular disease or alternatively they may be followed up in the neurology clinic.

8. The extent of diagnostic work up to be performed on a muscle biopsy will vary but must include histology, histochemistry and immunohistochemistry (Table 7).

Further investigations may be needed, directed by the biopsy appearance, including western blotting, enzymology and mitochondrial DNA analysis; a frozen sample should be stored at the time of biopsy to be available for such studies.

MINIMAL MUSCLE BIOPSY INVESTIGATIONS

Histology and histochemistry
- Haematoxylin & eosin, modified Gomori trichrome (morphologies),
- Oil red O (lipid),
- periodic acid-Schiff (glycogen),
- adenosine triphosphatase (9.4, 4.2, and 4.6) (fiber type)
- succinate dehydrogenase (SDH), Nicotinamide Adenine Dinucleotide Hydrogenase (NADH), cytochrome c oxidase(mitochondria)
- myophosphorylase (glycolysis),
- acid phosphatase (inflammation)

Immunohistochemistry (genetic/inflammation)
- Dystrophin, a, b, c and d sarcoglycans, dysferlin, caveolin-3, MHC-1, a-dystroglycan

European Journal of Neurology 2010, 17: 767–773

CONCLUSION

The nature of creatinine kinase (CK)

Common causes of CK elevation

Rhabdomyolysis and pathophysiology

Asymptomatic hyperCKemia (>1.5 times of normal)
- Causes
- Investigation
- Diagnostic values