HYPERCKEMIA: FROM ASYMPTOMATIC TO CLINICAL PHENOTYPE

Marianne de Visser, MD

Dept. of Neurology

Amsterddam University Medical Centre, location Academic Medical Centre

Amsterdam, The Netherlands

Email address: m.devisser@amsterdamumc.nl

Disclosures

- On site PI Pharnext (CMT)
- Co-investigator FORCE trial (postpolio syndrome)
- Member Adjucation Committee Bristol-Myers Squibb Company (myositis)
- Member Data Safety Monitoring Board AveXis (SMA)
- Member Data Safety Monitoring Board Dynacture (centronuclear myopathy)

Learning objectives

At the end of this lecture the learner

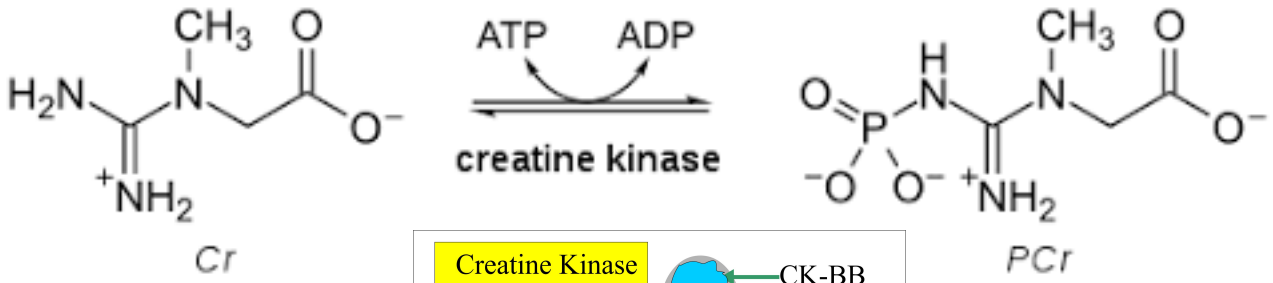
- knows how to evaluate patients with asymptomatic hyperCKemia
- knows how to evaluate patients with symptomatic hyperCKemia
- has insight into the clinical manifestations of diseases with markedly elevated CK

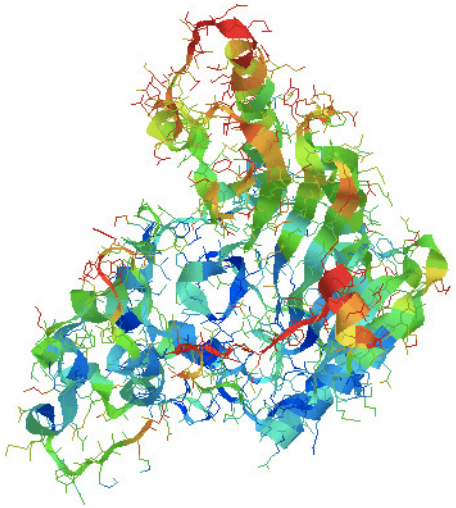
Outline

- Defining HyperCKemia
- Causes of HyperCKemia
- Diagnostic Evaluation of HyperCKemia
- Risk of Malignant Hyperthermia

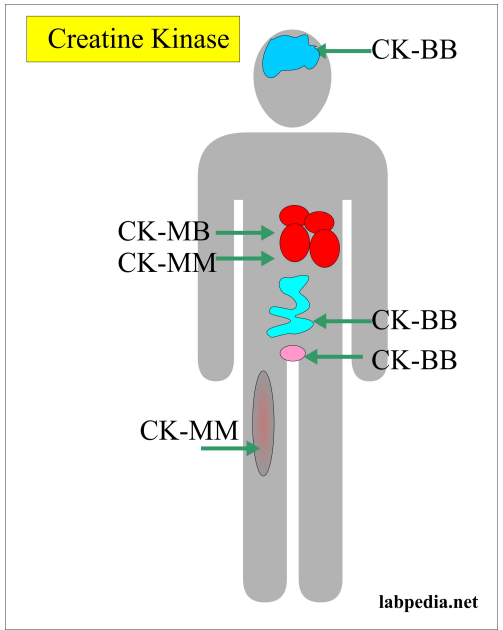
What is creatine kinase?

Creatine kinase (CK) is an enzyme playing an important role in the energy metabolism of cells.





CK activity is by far the highest in skeletal muscle



When do we speak of hyperCKemia?

CK varies amongst ethnicities.

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
hyper-CK-emie*	≥ 325	≥ 504	≥ 621	≥ 1201

* Hyper-CK-emie is 1,5 the upper limit of the reference values

Brewster et al. 2007

	n	2.5–97.5 Percentile CK U/L
Reference individuals		
Women	3737	37–207
Men	3056	49–367

Lilleng et al. 2011

CK and exercise

- CK activity rises after exercise or heavy manual labour.
- Serum CK may increase as 30 x ULN < 24 hours of strenuous physical activity, then slowly decline over the next 7 days.
- Degree of CK elevation depends on the type and duration of exercise (greater elevation in those who are untrained).
- In assessing asymptomatic or minimally symptomatic hyperCKemia, the test should be repeated after 7 days without exercise.
- A large Norwegian study (Lilleng et al 2011) showed that repeat CK in people with incidentally discovered elevated CK was normal after 3 days of ‘rest’ in 70-90% of the cases.

HyperCKemia due to other causes than neuromuscular

Table 1 Causes of hyperCKemia (examples).

Inherited and acquired myopathies
Inherited and acquired neuropathies (including motor neuron diseases, radiculopathies)
Medications (e. g., statins, fibrates, beta blockers, angiotensin-II receptor blockers, clozapine, hydroxychloroquine, isotretinoin, colchicine)
Physical exertion, sports
Trauma (e. g., fall, crush injury)
Seizures
Muscle cramps (paraphysiological or symptomatic)
Iatrogenic (e. g., intramuscular injection, EMG examination, surgery)
Pregnancy
Ethnicity
Surgical procedures
Toxins (e. g., alcohol, heroin, cocaine)
Endocrine (e. g., diabetes mellitus, hypothyroidism, hypoparathyroidism, acromegaly)
Viral infections
Metabolic (hypokalemia, hyponatremia, hypophosphatemia)
Myocardial infarction / chronic cardiac disease
Obstructive sleep apnea syndrome
Neuroacanthocytosis
macro-CK
Renal disease
Celiac disease
Connective tissue disorders
Malignancies

Statins and hyperCKemia

- Asymptomatic hyperCKemia – may increase resting CK by 50% (high CK 1.6 per 1000 patients, mild to moderate 6.4 per 1000 patients)

Statin-Associated Muscle Symptoms (10-20%)

- Rhabdomyolysis (CK >100-fold ULN) - 1.5 for each 100,000 people taking statins
- Myalgia or mild hyperCKemia (<5× ULN);
- Self-limited toxic statin myopathy (CK 10-100 ULN)
- Myositis or immune-mediated necrotizing myopathy with HMG-CoA reductase antibodies and CK 10-100× ULN.

HyperCkemia with a neuromuscular cause

- Asymptomatic

- Paucisymptomatic

  Non-specific symptoms
  - mild myalgias, cramps, fatigue
  - absence of severe exercise intolerance
  - subjective muscle weakness, no evidence of weakness on examination

- Symptomatic

Evaluation: History is cornerstone of diagnosis

- Medical history is the cornerstone of diagnosis (70-90%)
  - Symptoms
  - Age at onset
  - Age of developmental milestones achieved
  - Maximal functional abilities achieved (i.e. sitting; walking)

- FAMILY HISTORY can be instrumental for establishing a diagnosis

History cont'd

Onset and course of the disease

- Subacute; progressive: Myositis
- Slowly progressive: Muscular dystrophies/other hereditary myopathies

Time of onset

- Congenital: Congenital myopathies, muscular dystrophies
- Childhood: Muscular dystrophies
- Juvenile: Dermatomyositis
- Adult: Myositis, Myofibrillar myopathies
- Late: Inclusion body myositis

Clinical presentation of nmd with hyperCKemia

Bulbar weakness – IBM, Bulbospinal muscular atrophy, ALS

Limb-girdle syndrome – Dystrophinopathy, LGMDs, congenital muscular dystrophy, DM2, Pompe's disease, SMA type 3

Distal muscle weakness – Dysferlinopathy, Anoctaminopathy, Myofibrillar myopathies

Muscular dystrophy with contractures – Emery-Dreifuss MD (X-linked or AD)

Symmetrical or asymmetrical muscle weakness – IBM

Rhabdomyolysis – Mc Ardle's disease, CPT2 deficiency, mitochondrial

Associated signs and symptoms

- Myotonia
- Cardiac involvement
- Contractures
- Calf hypertrophy
- Rippling muscles
- Fasciculation
- Myalgia
- Exercise intolerance
- Skin abnormalities
- Dysmorphic stigmata
- Lung involvement, arthritis

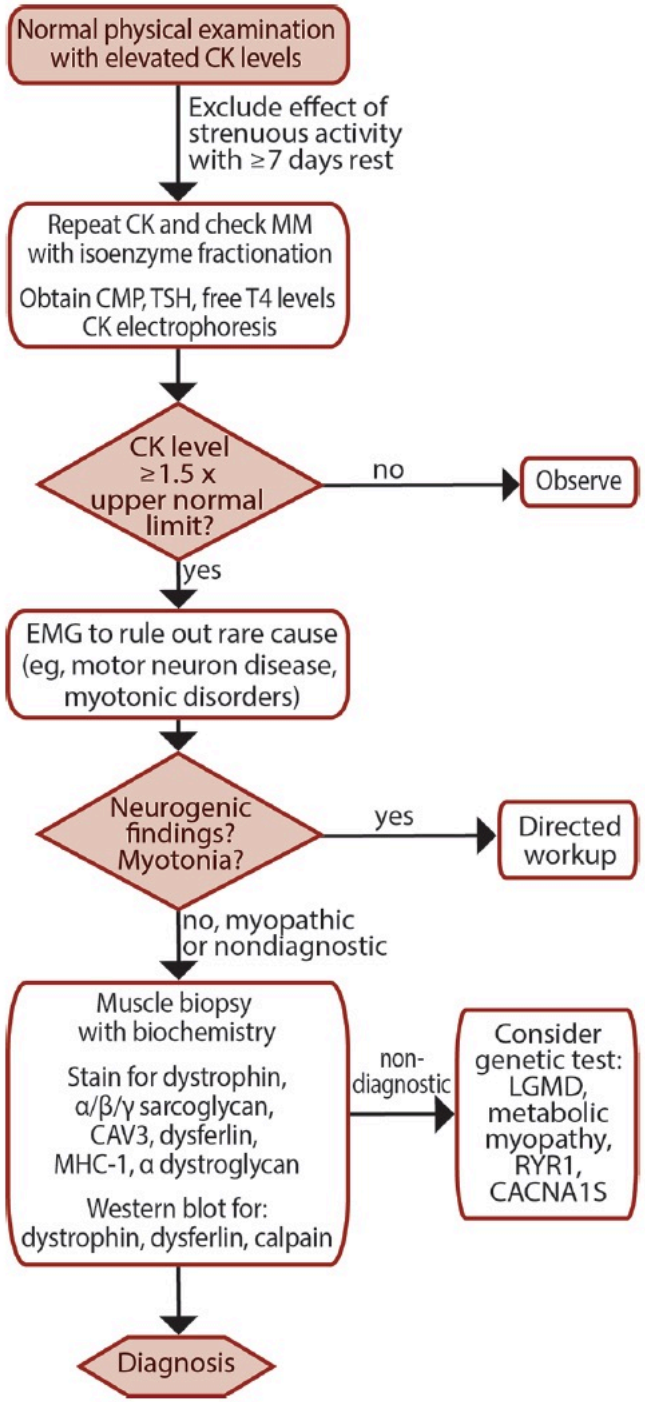
Symptomatic hyperCKemia

Muscular dystrophies	Dystrophinopathies (Duchenne, Becker, carrier)
	- LGMD R1 – calpain3-related
	- LGMD R2 – dysferlin-related
	- LGMD R11 - ANO5-related
	- LGMD R9 – FKRP-related and other glycosylation defects of alpha dystroglycan (PMOT1, POMT2, fukutin, POMnGT1, POGLUT1, DAG1
	- Other LGMDs: telethonin, TRIM32, plectin, TRAPPC11, titin, GMPPB, ISPD, POPDC1, LAMA2
Metabolic myopathies	Pompe's disease/Danon disease
	CPT2 deficiency
	Mc Ardle disease
Myotonic syndromes	DM2
Myositis, IBM excluded	DM, Necrotizing myopathy, overlap myositis, antisynthetase syndrome
Neurogenic disorders	Bulbospinal muscular atrophy
	Motor neuron disease (ALS)
	SMA type 3

Asymptomatic hyperCKemia

Muscular dystrophies	Dystrophinopathies (Duchenne, Becker, carrier)
	LGMDs
	- LGMD R1 – calpain3-related
	- LGMD R2 – dysferlin-related
	- LGMD R11 - ANO5-related
	- LGMD R9 – FKRP-related
Other hereditary myopathies	Rippling muscle syndrome/caveolinopathy
Metabolic myopathies	Pompe's disease
	Danon disease
	CPT2 deficiency
	Mc Ardle disease
Myotonic syndromes	DM2
Neurogenic disorders	Bulbospinal muscular atrophy
	SMA type 3

Diagnostic Algorithm for Asymptomatic HyperCKemia



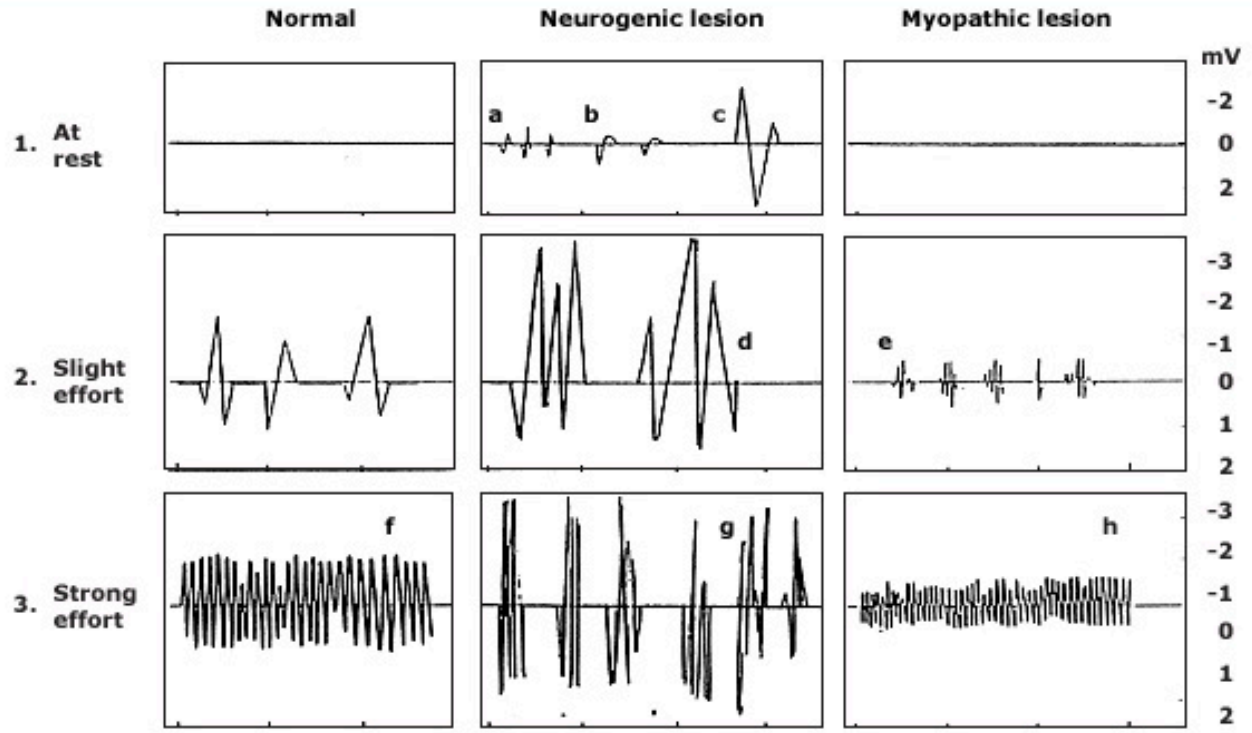
Silvestri and Wolfe
Practical Neurology 2019

Ancillary investigations for evaluation of hyperCKemia

- CK, serology tests
- EMG
- Imaging – MRI/ultrasound
- Muscle biopsy, skin biopsy
- DNA analysis (singe gene testing -> targeted screening, WES)

Electromyography

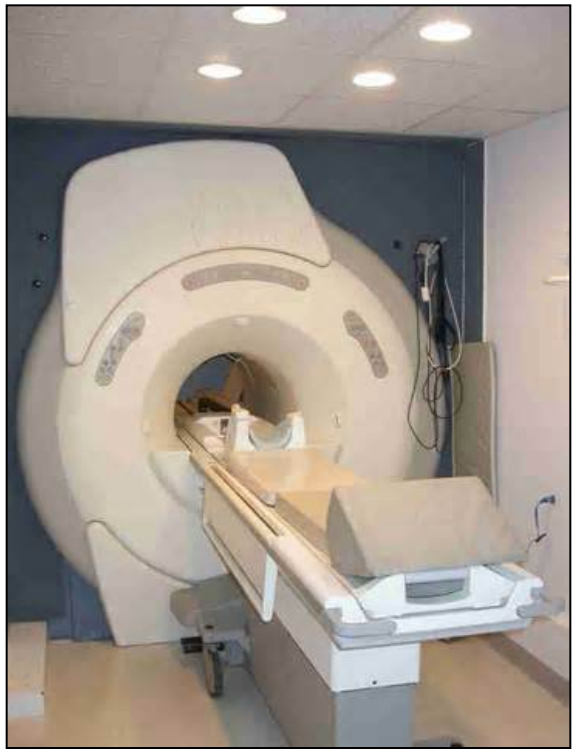
Electromyography* comparing normal, neurogenic, and myopathic features

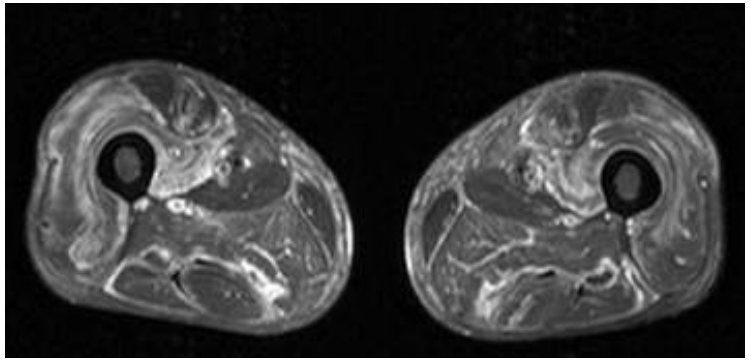


1. At rest (spontaneous activity): a. fibrillations, b. positive sharp waves, c. fasciculation.
2. Slight effort (motor unit potentials): d. giant polyphasic, e. BSAPS (brief-small-abundant polyphasic).
3. Strong effort (interference pattern): f. full, g. reduced units, h. reduced amplitude.

* helpful in selecting denervated muscles in radiculopathies (myotomal), mononeuropathies (distal to lesion), generalized neuropathies (distal muscles), and myopathies

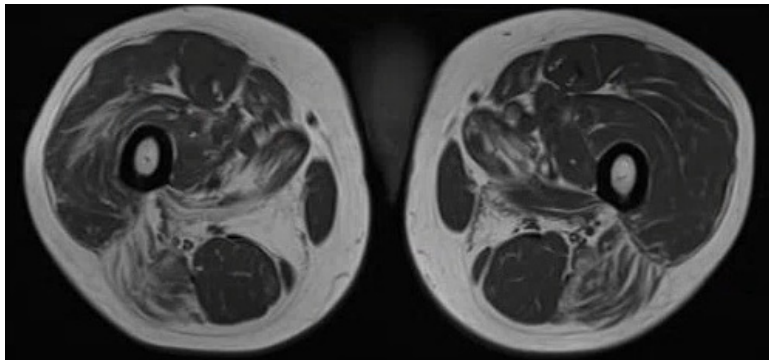
Muscle imaging

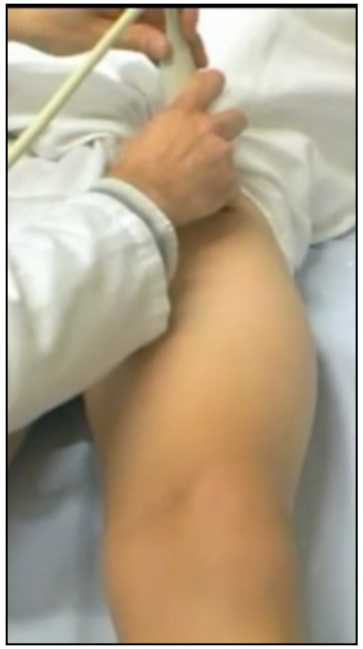


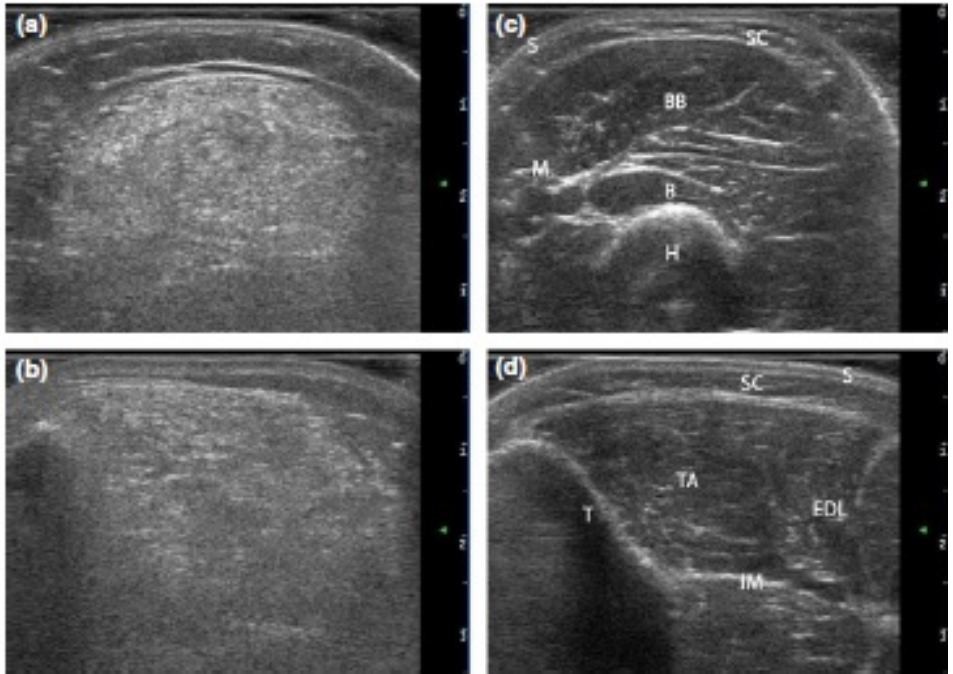


Myositis

LGMD2L
(ANO-5)







EDMD

Biceps brachii muscle

Tibialis ant. muscle

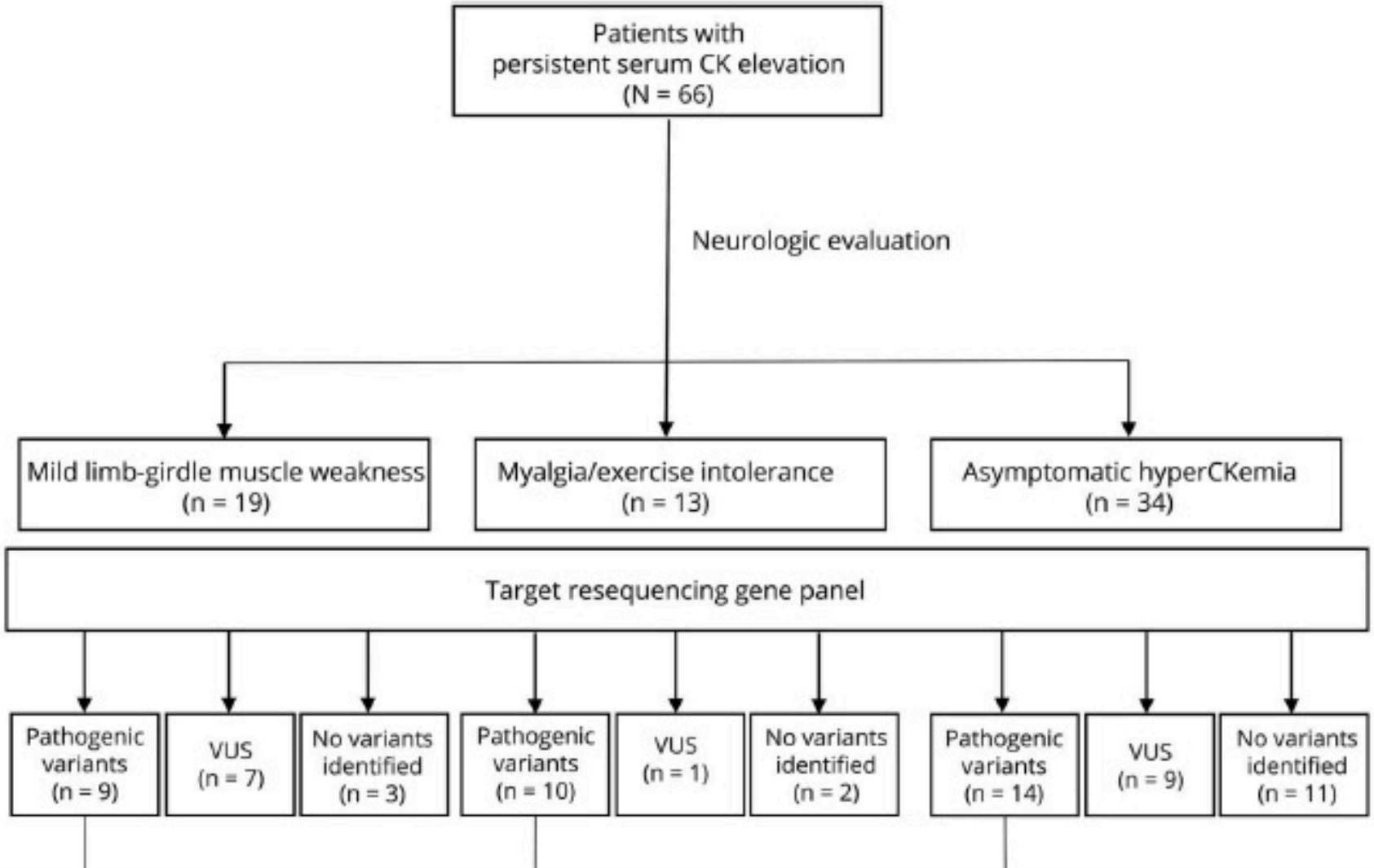
Muscle biopsy

- Open or needle muscle biopsy
- Histology (H&E)
- Enzyme histochemistry (e.g., ATPases/myosin isoforms, oxydative enzymes, COX)
- Immunohistochemistry (e.g., sarcolemmal proteins, inflammatory markers)

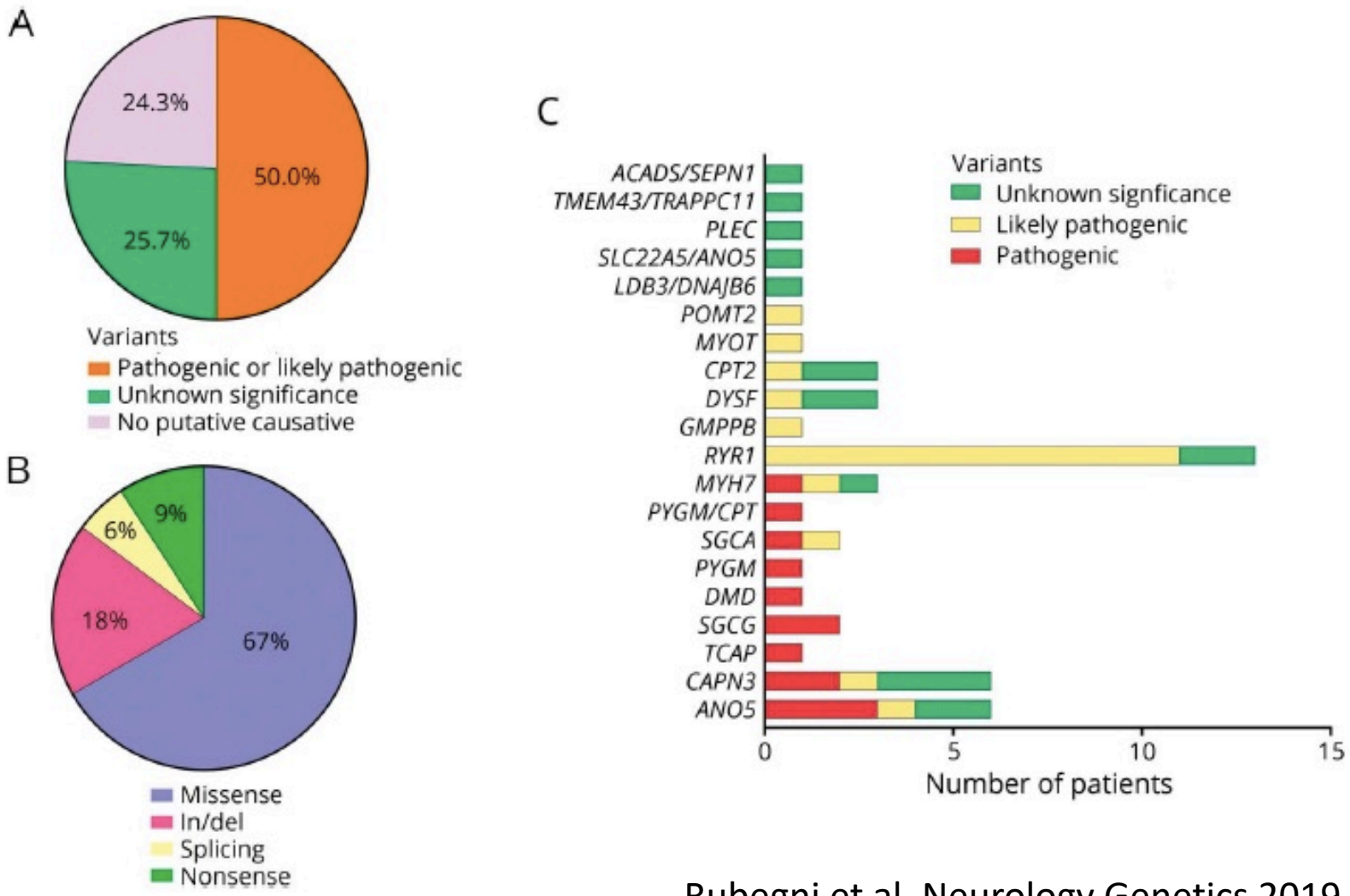
Evaluation of a/paucisymptomatic hyperCKemia by NGS

Figure 1 Flowchart of patients' enrollment and results of genetic testing

Rubegni et al.
Neurology Genetics 2019



Diagnostic rates and molecular results



Rubegni et al. Neurology Genetics 2019

Asymptomatic hyperCKemia and risk for malignant hyperthermia

- Family history
- Few large studies:
  - Weglinski et al. (1997) - 24/49 (49%) of patients with asymptomatic hyperCKemia had positive contracture tests.
  - Malandrini et al. (2008) found one susceptible and one equivocal subject in 37 patients with asymptomatic hyperCKemia.