

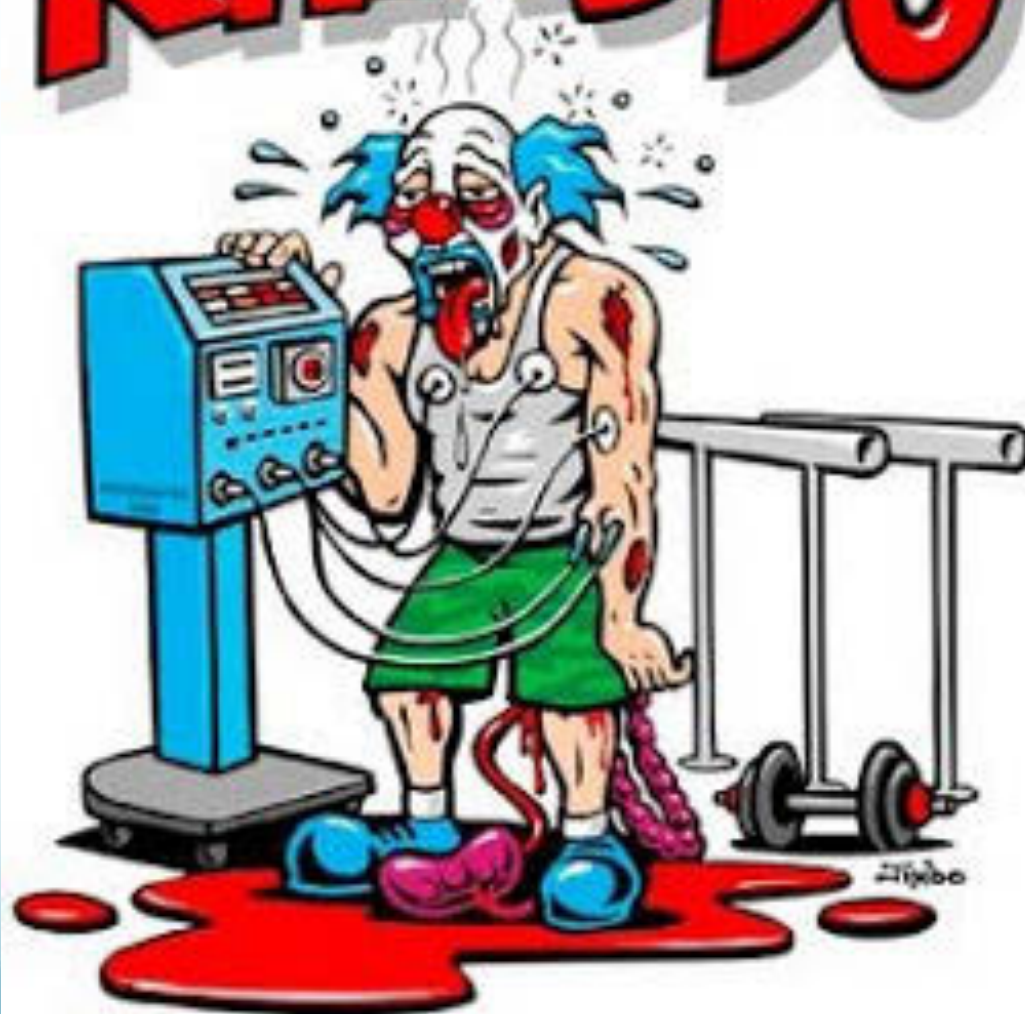
# Current Concepts in Rhabdomyolysis

Sydney Neurophysiology Meeting 2014

# outline

- Quick overview of rhabdo
  - History
  - Causes
  - Clinical
- Investigations – which ones/what order?
- Role of NGS
- ?Role of steroids
- Cases

# RHABDO



# History



# Clinically

- Myalgia
- Weakness
- Pigmenturia



# Clinically



Asymptomatic  
HyperCKaemia

- High Potassium
- Cardiac arrhythmia
- ARF
- DIC

# Differential Diagnosis

- Myositis
- Muscular dystrophy
- Endocrine disorders



# Causes



**"How do you like the new aerobics instructor?"**



Type	Causes
<b>Exertional rhabdomyolysis</b>	<a href="#">Extreme physical exercise (particularly when poorly hydrated), delirium tremens (alcohol withdrawal), tetanus, prolonged seizures or status epilepticus[1][2]</a>
<b>Crush</b>	<a href="#">Crush syndrome, blast injury, car accident, physical torture or abuse, or confinement in a fixed position such as after a stroke, due to alcohol intoxication or in prolonged surgery[1][2]</a>
<b>Blood supply</b>	<a href="#">Arterial thrombosis (blood clots forming locally) or embolism (clots or other debris from elsewhere in the body), clamping of an artery during surgery[1][2]</a>
<b>Metabolism</b>	<a href="#">Hyperglycemic hyperosmolar state, hyper- and hyponatremia (elevated or reduced blood sodium levels), hypokalemia (low potassium levels), hypocalcemia (low calcium levels), hypophosphatemia (low phosphate levels), ketoacidosis (e.g., in diabetic ketoacidosis) or hypothyroidism (abnormally low thyroid function)[1][2][6]</a>
<b>Body temperature</b>	<a href="#">Hyperthermia (high body temperature) and heat illness, hypothermia (very low body temperature)[1][2]</a>
<b>Drugs and toxins</b>	<p>Many medications increase the risk of rhabdomyolysis.[7] The most important ones are:[1][2][6]</p> <p><a href="#">Statins and fibrates, both used for elevated cholesterol, especially in combination: cerivastatin (Baycol) was withdrawn in 2001 after numerous reports of rhabdomyolysis.[8] Other statins have a small risk of 0.44 cases per 10,000 person-years.[9] Previous chronic kidney disease and hypothyroidism increase the risk of myopathy due to statins. It is also more common in the elderly, those who are severely disabled, and when statins are used in combination with particular other medicines, such as ciclosporin.[8][9]</a></p> <p><a href="#">Antipsychotic medications may cause neuroleptic malignant syndrome, which can cause severe muscle rigidity with rhabdomyolysis and hyperpyrexia</a></p> <p><a href="#">Neuromuscular blocking agents used in anesthesia may result in malignant hyperthermia, also associated with rhabdomyolysis</a></p> <p>Medications that cause <a href="#">serotonin syndrome</a>, such as SSRIs</p> <p>Medications that interfere with potassium levels, such as <a href="#">diuretics</a></p> <p>Poisons linked to rhabdomyolysis are <a href="#">heavy metals and venom from insects or snakes</a>. <a href="#">Hemlock may cause rhabdomyolysis, either directly or after consuming quail that have fed on it.[1][6]</a> <a href="#">Haff disease is rhabdomyolysis after consuming fish: a toxic cause is suspected but has not been proven.[10]</a></p> <p>Drugs of abuse, including:</p> <p><a href="#">alcohol, amphetamine, cocaine, heroin, ketamine, LSD and MDMA (ecstasy)[1][6]</a></p>
<b>Infection</b>	<a href="#">Coxsackie virus, influenza A virus and influenza B virus, Epstein-Barr virus, primary HIV infection, Plasmodium falciparum (malaria), herpes viruses, Legionella pneumophila and salmonella[1][2][6]</a>
<b>Inflammation</b>	Autoimmune muscle damage: <a href="#">polymyositis, dermatomyositis[1][6]</a>

# CAUSES

Acquired

Genetic

- Glycogenoses
- Lipid storage Disorders
- Mitochondrial Disorders
- Muscular dystrophies
- LPIN1 mutations/RYR1 mutations/AMACR defic

Traumatic

- Crush injury
- Electrical injury
- Prolonged immobilisation

Non-traumatic

Exertional

- Extreme exertion
- Status epilepticus
- Severe dystonia

Non-exertional

- Drugs
- Toxins
- Infections
- Electrolyte disorder
- IIM's

# Triggers to consider genetic cause

- Recurrent episodes
- Unprovoked episodes
- Positive family history
- Concomitant exercise intolerance or muscle cramps

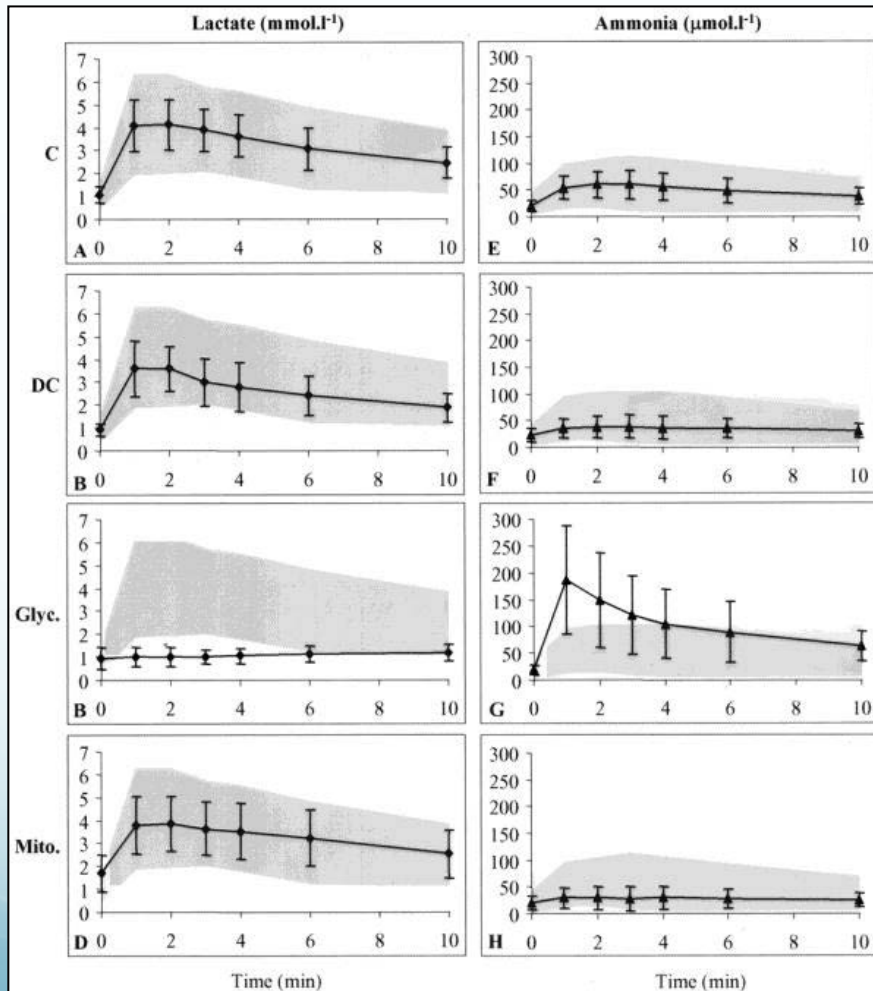
# Investigations – 1<sup>st</sup> line

- CK > 10 X ULN
  - Degree CK  $\propto$  degree muscle injury
  - Peaks 24-72hrs
  - Declines 3-5 days
- EUC/LFT's/ABG (pH)/CMP
- TFT's, BSL
- ECG

# Investigations – 2<sup>nd</sup> Line

- If 1<sup>st</sup> episode, no sig family history or personal history of myalgia's, exercise intolerance or cramps
  - **No further investigation required**
- If underlying metabolic myopathy suspected
  - Aerobic Forearm test
  - Fasting carnitine/Acyl-carnitine profile
    - Enzyme activity measurements in lymphocytes
  - FGF-21
- Genetic analysis – targeted vs Chip
- Muscle Biopsy 6/52 after episode rhabdo

# Aerobic Forearm Test



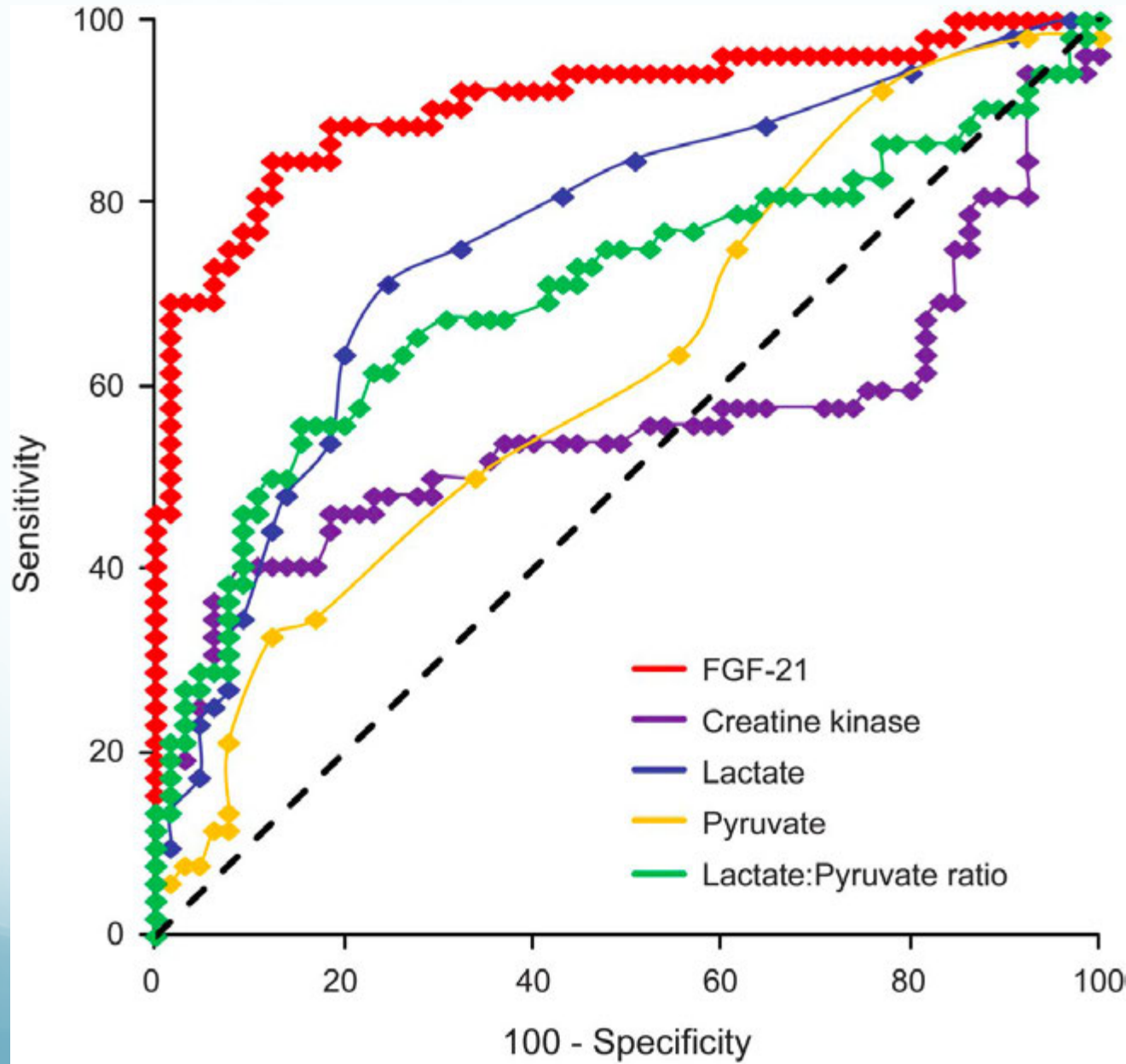
## A non-ischemic forearm exercise test for the screening of patients with exercise intolerance.

Hogrel, J-Y; Laforet, P; Ben Yaou, R; Chevrot, M; Eymard, B; MD, PhD; Lombes, A; MD, PhD

Neurology. 56(12):1733-1738, June 26, 2001.

Figure 2 . Mean results for lactate (A-D) and ammonia (E-H) in the four groups of controls and patients. The shaded areas correspond to the reference limits defined as  $\pm 2$  SD around the mean of the control subjects.

# FGF-21



CM Sue  
and  
colleagues;  
Neurology®  
2013;81:1-  
8



# CLINICAL AND MOLECULAR CHARACTERIZATION OF PATIENTS WITH REPEATED EPISODES OF RHABDOMYOLYSIS

M. Cabrera; R. Ghaoui; D. Mourdant; P.J. Lamont; N. Clarke;  
N. Laing.

- Presented at WMS (Berlin 2014)
- Investigated 50 patients with rhabdo
- Used panel of 227 known NM genes
- Confirmed with Sanger sequencing

# CLINICAL AND MOLECULAR CHARACTERIZATION OF PATIENTS WITH REPEATED EPISODES OF RHABDOMYOLYSIS

M. Cabrera; R. Ghaoui; D. Mourdant; P.J. Lamont; N. Clarke;  
N. Laing.

- Muscle biopsy unhelpful in all these unsolved cases
- Underlying molecular diagnosis found in 28%, with a possible cause for an additional 16%
  - (33% in multiple episodes vs 14% in single episode)
  - Found in 80% of cases with a positive family history
- Most frequent causes were CPTII and RYR1 mutations

# ? Evidence for Steroids

- Case reports in
  - Clarkson's disease (massive capillary leak)
  - Acute adrenal insufficiency
  - Alcohol-induced rhabdo

But

- Steroids can cause rhabdo
  - in DMD
  - Anabolic steroid injection – localised deltoid rhabdo
  - Myeloma patient
  - ICU patients on muscle relaxant+ steroids

# Case 1

- 43 year mother-of-five
- Presented with 3 episodes of rhabdo
- Bg 14 years post-exercise myalgia
- No sig PMHx
- 5 C-sections under spinal, no GA's

# Developmental Hx DD

- Normal delivery and motor milestones
- Good at sport in Primary School
- High school – aerobics, netball and weight training without myalgia's, cramping or myoglobinuria
- Onset sx after birth first child age of 29 yrs (stopped all formal sport)
- Noticed bilateral calf pain after 30 min walk
- No pain during exercise, but onset after exercise and would last hours

# rhabdo

- 1<sup>st</sup> episode after usual walk, developed calf pain after a few hrs, then pain spread superiorly up thighs, back and shoulders, then myoglobinuria
- 2<sup>nd</sup> attack at time of colonoscopy when fasting – developed pain and stiffness in legs before procedure,
- 3<sup>rd</sup> episode again related to usual walk
- No family history, clinical examination normal

# Investigations

- Fasting carnitine/Acyl carnitine
  - Normal total and free Carnitine,
  - Normal Acetylcarnitine

But

- Tetradecanoylcarnitine 7.1 ( $<0.7$ )
- Consistent with VLCAD deficiency
  - (Prof Christodoulou/A/Prof Kevin Carpenter)

Confirmed mutation in Acyl-CoA Dehydrogenase, VLC gene (ACADVL)



# Case 2

- 22 yr man
- 3 episodes rhabdo
- 7-8yr hx of muscle cramping during intense exercise
- Worst symptoms when surfing

# Case 2

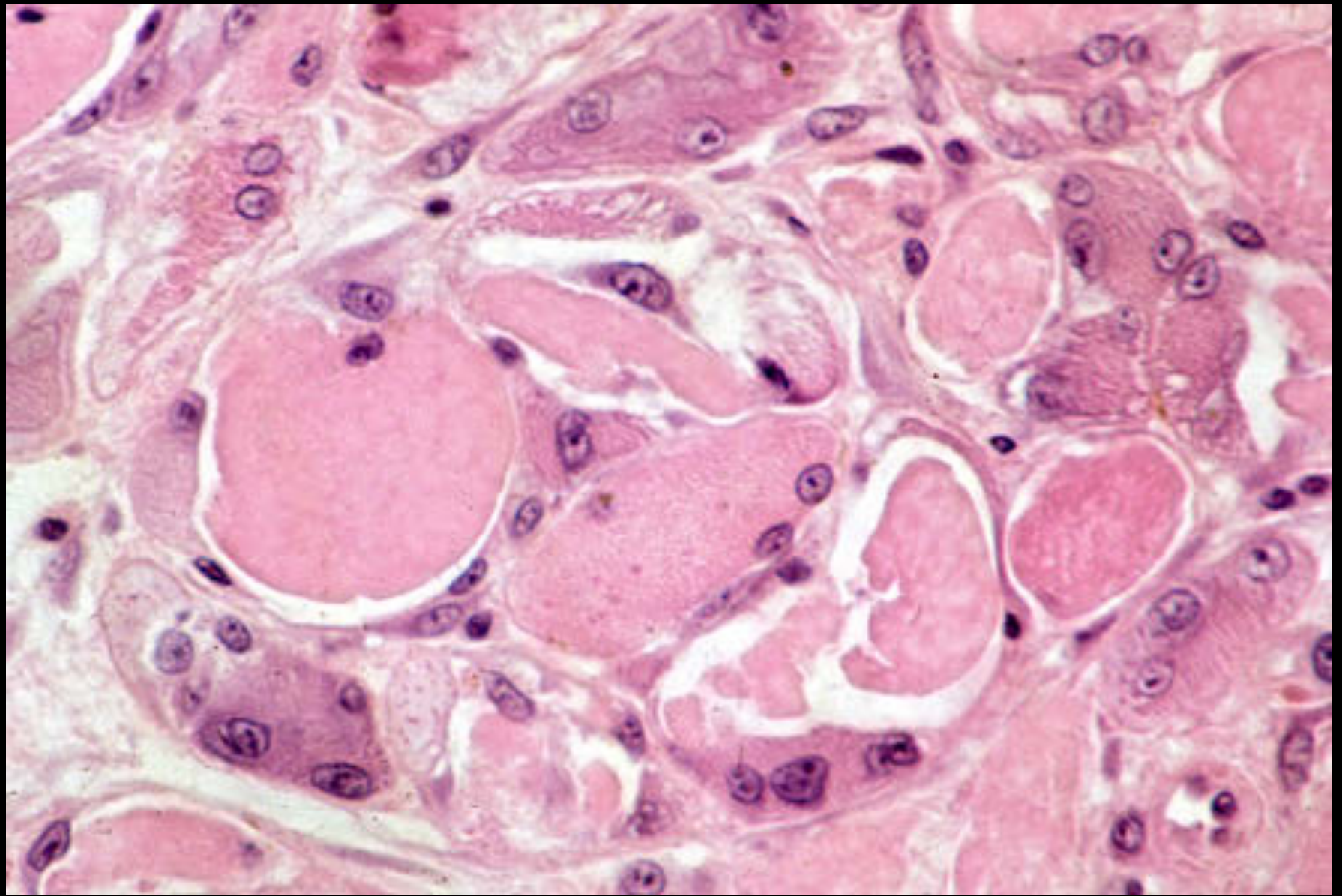
- Hx typical of glycogen storage disorder
- +ve aerobic forearm test
- Common mutation found in McArdle's disease

# Case 3

- 46 year old man
- Unwell for 1/52 with fevers/myalgia's
- Presented with progressive weakness and swelling
- CK 25,000

# Initial progress

- Initial thought was viral-induced rhabdo
- Treated with IVF
- CK reduced only slightly
- Myalgia's/muscle swelling migrated to different muscle groups over a week



# Differentials

- Severe ongoing rhabdo ?cause
- ?Necrotising myositis
- ?DM

# Diagnostic stain

- MAC stain added
  - Positive!
- Dermatomyositis



# Take home messages

- Need to recognise rhabdo
- Familiar with clues for underlying cause
- Familiar with appropriate investigations
- Increasing role of NGS - especially if:
  - recurrent episodes
  - family history



# Acknowledgments



Professor Frank Mastaglia

Professor Carolyn Sue

Professor Phillipa Lamont

Professor Nigel Laing

Dr Mark Davis

Dr Helen Young

Professor Kathy North

Dr Christina Liang

Dr Vicki Fapien

Dr Rei Junckerstorff and All referring Doctors

