35 year old female with muscle cramps after a marathon

35 year old female

Well, no health concerns

Training for her first marathon

Couple of episodes of muscle cramping

Entered the London Marathon

35 year old female

Given a massage and a cold towel down and sent back to her hotel

Muscle cramps and vomiting all through the night

Passed a small amount of very dark urine (x1)

Next morning was taken by ambulance to hospital

35 year old female

What tests should the emergency department team request?

Urea	15.3 mmol/L ↑	(1.7-8.3)
Creatinine	256 umol/L ↑	(49-92)
Sodium	139 mmol/L ✓	(135-145)
Potassium	4.5 mmol/L ✓	(3.5-5.1)
Estimated GFR	19 ml/min/1.73sqm	

What other test would you request?

Creatine kinase	149,573 IU/L ↑↑	(26-140)

What is the diagnosis?

Rhabdomyolysis with renal impairment

35 year old female

What tests should the emergency department team request?

Urea	15.3 mmol/L ↑	(1.7-8.3)
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What other test would you request?

Creatine kinase	149,573 IU/L ↑↑	(26-140)

What is the diagnosis?

Rhabdomyolysis with renal impairment

35 year old female

How would you treat this?

Dialysed for 2 weeks

Careful fluid and electrolyte balance

What is your differential diagnosis for the underlying cause?

Causes of rhabdomyolysis

Acquired

Crush injuries – earthquakes

Infection - myositis

Ischemia-reperfusion - thrombus, compression

Drugs – cocaine

Medications – statins; volatile anaesthetics

Exertional – marathons, crossfit, weightlifting

Genetic

Glycogen storage disorders (GSD V, VII, IIIa)

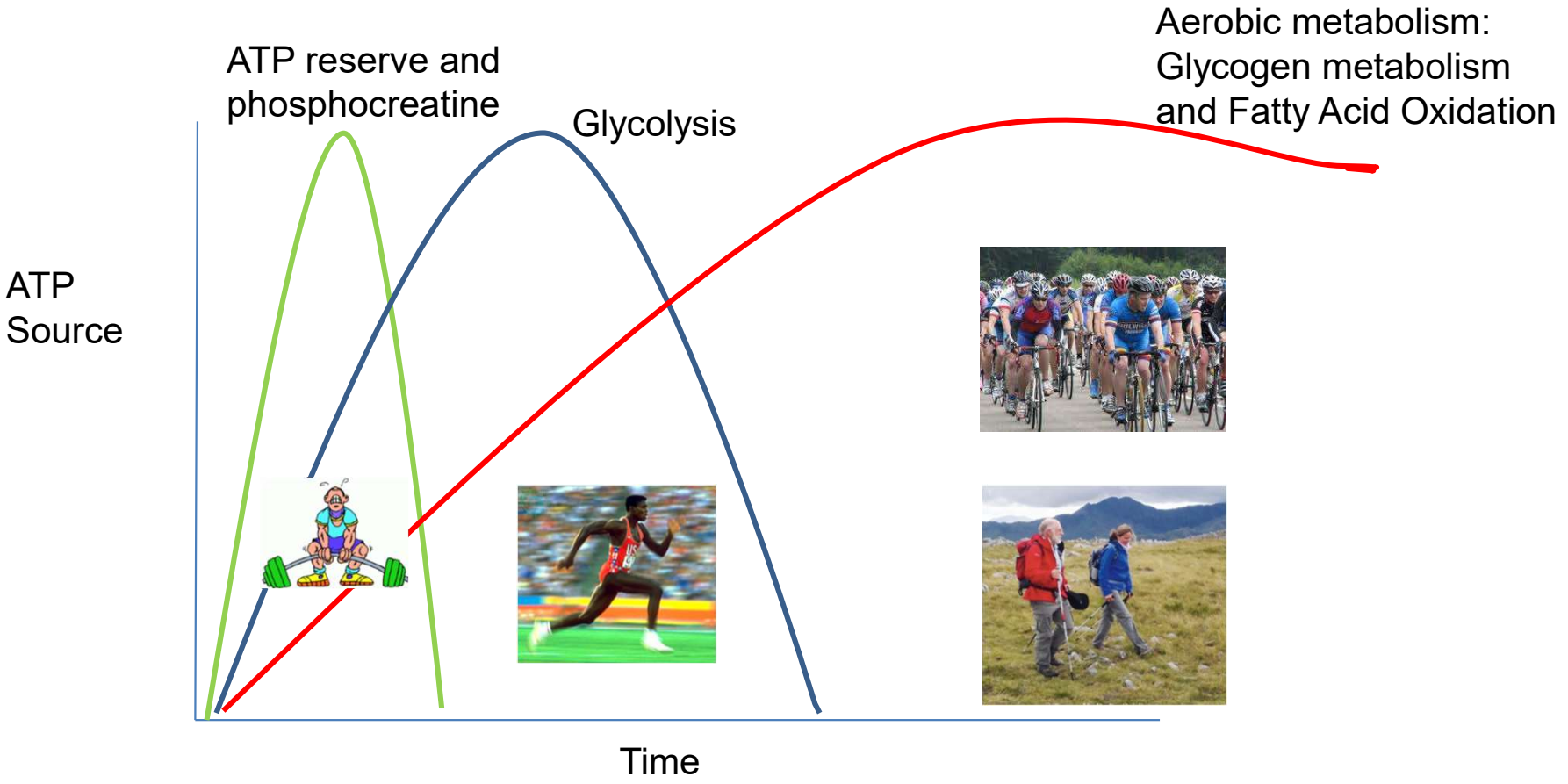
Fatty acid oxidation disorders

Disorders of phospholipid metabolism (LPIN)

Others – RYR1, CACNA1S, STAC3, CAV3

London adult clinic – 2 year review of 51 new cases:
37% unaccustomed exercise
20% GSD V (McArdle)
20% CPT2 deficiency
23% RYR1 variants

Muscle energy metabolism



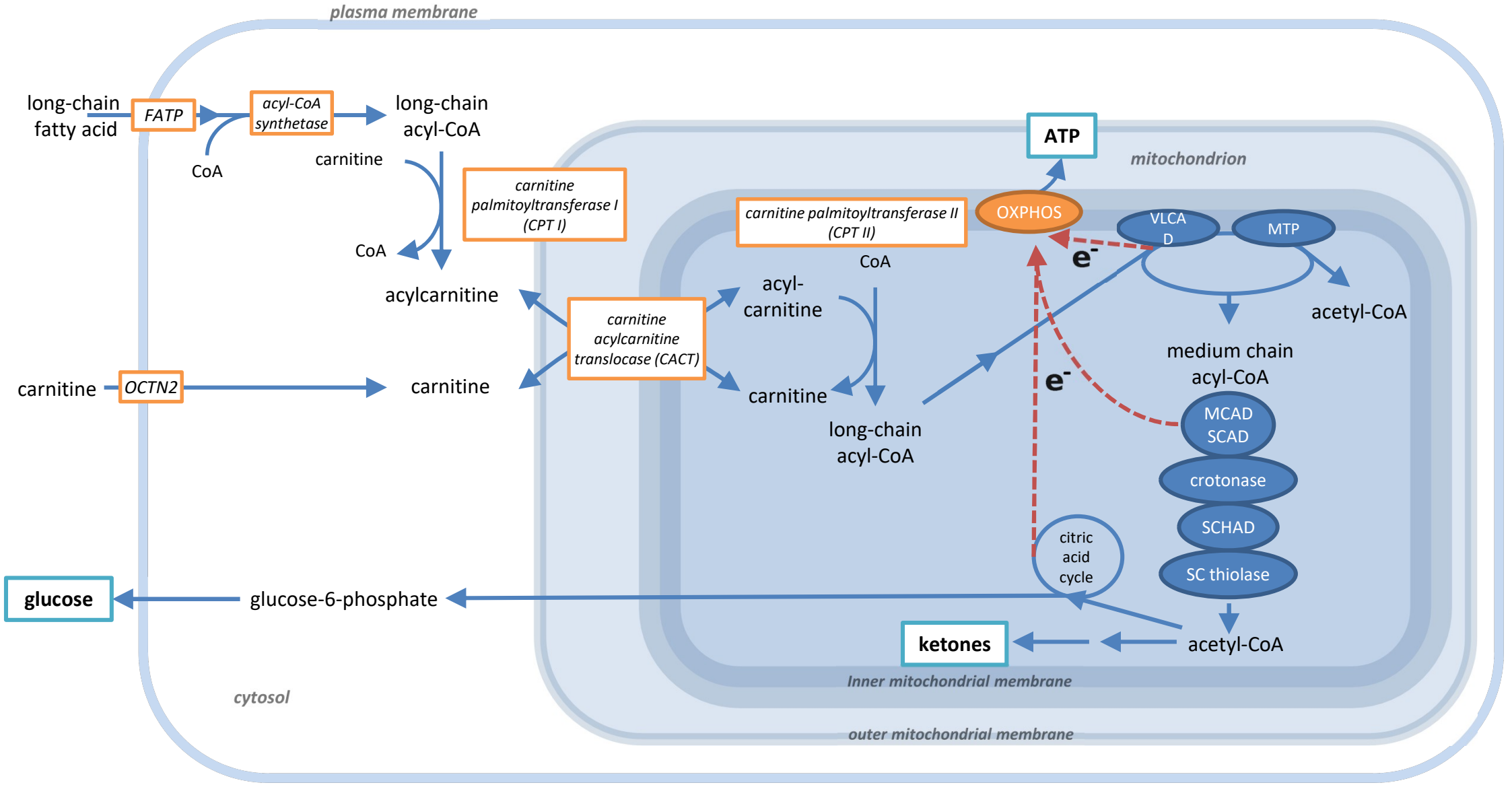
35 year old female

How would you investigate?

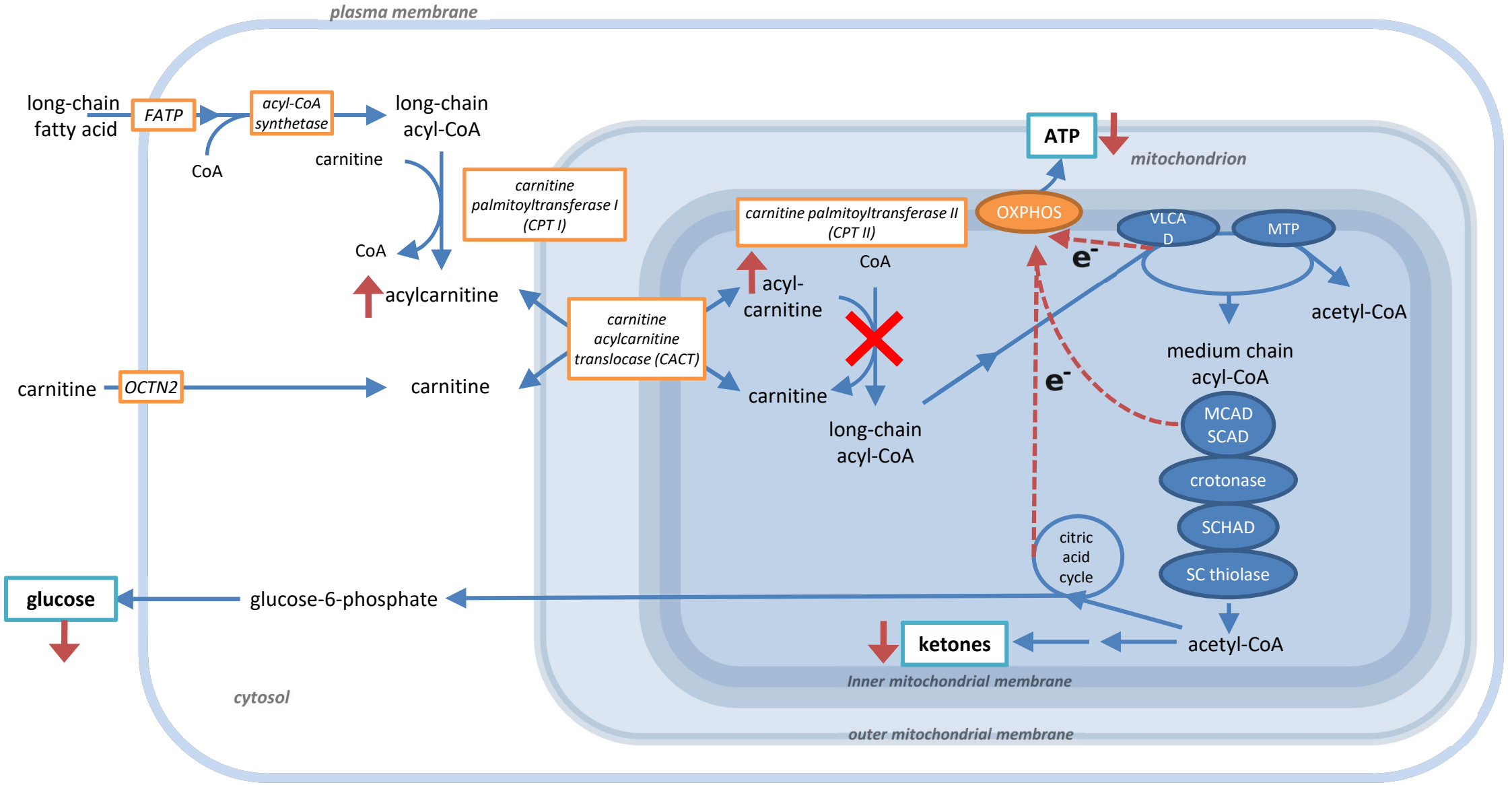
Muscle biopsy	?mild increase in lipid content
Plasma acylcarnitine profile	Raised C14 - C18 carnitine esters: predominantly C16=0.48 µmol/l (≤ 0.28) and C18:1=0.74 µmol/l (≤ 0.40). Free carnitine = 37 µmol/L (16-55)
Fibroblast studies (skin biopsy)	
Fatty acid oxidation flux	normal
CPT2 activity	1.4 nmol/mg/min (17% of control activity) ↓
Genetic analysis	p.[Ser113Leu] homozygous mutations of *CPT2* gene

→ **Carnitine palmitoyltransferase II deficiency**

Mitochondrial fatty acid β-oxidation

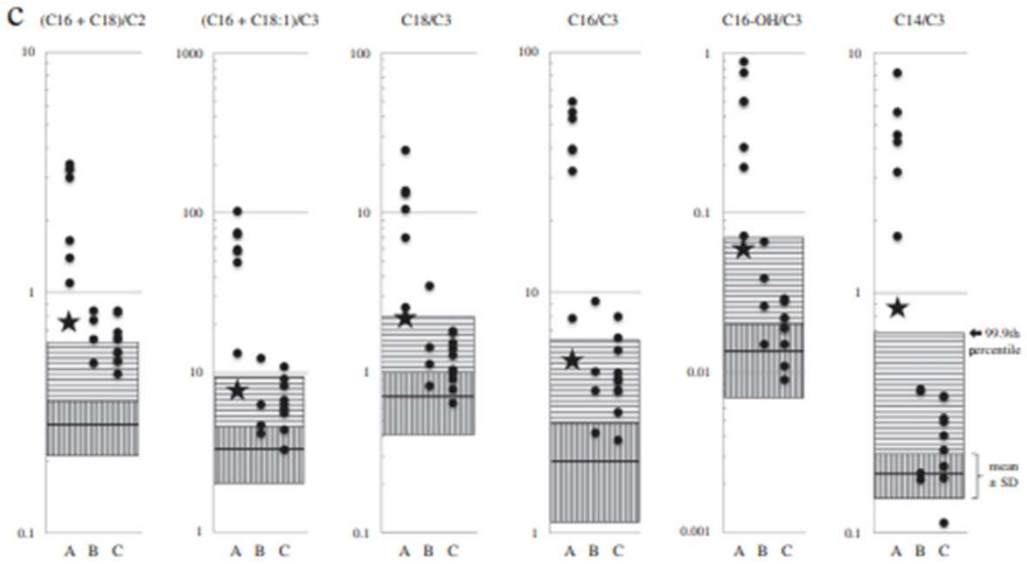


Mitochondrial fatty acid β-oxidation



Plasma vs dried blood spot

- CPT-II deficiency may be missed in DBS
- Acylcarnitine ratios in DBS may be helpful



A = CPT-II def (NBS)
B = heterozygotes
C = control
* = FN DBS

Molecular Genetics and Metabolism 122 (2017) 67–75

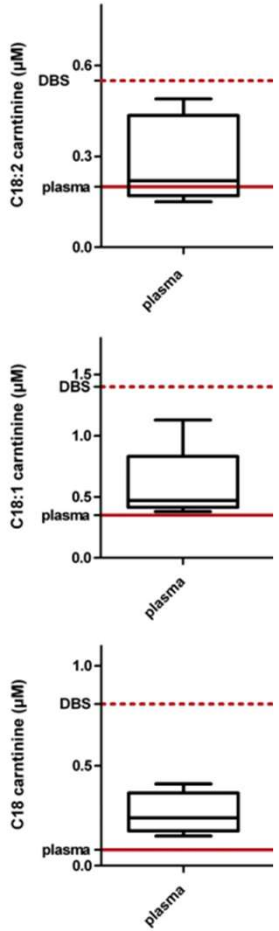
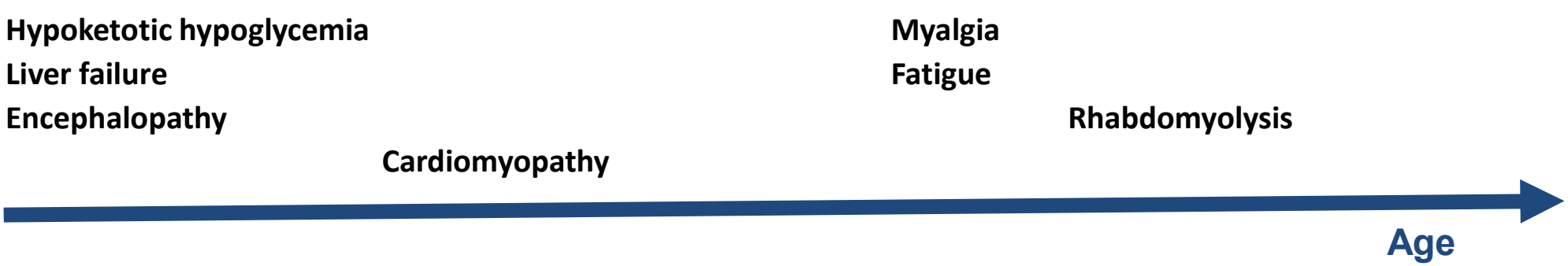


Fig. 3. Box-plots for C18:2-carnitine, C18:1-carnitine and C18-carnitine in plasma and DBS in four patients diagnosed with CPT-2 deficiency. Straight line represents 95th percentile of (age related) controls in plasma. Dotted line represents 95th percentile of (age related) controls in DBS.

M.G.M. de Sain-van der Velden et al. / Molecular Genetics and Metabolism 110 (2013) 116–121

Long-chain Fatty Acid Oxidation Disorders (CPT2, VLCAD, TFP, LCHAD deficiencies)



35 year old female

What treatment would you advise her?

Avoid / limit precipitants – fasting, fever / infection, prolonged exercise, anaesthesia

Give an emergency regimen (fluids and glucose / dextrose)

Other options for more severe childhood onset cases

- *Provide regular calories (frequent daytime feeds, overnight pump feed)*
- *Restrict dietary (long chain) fat*
- *Supplement with medium chain triglyceride & fat-soluble vitamins*
- *Supplement with uncooked cornstarch*
- *Supplement with triheptanoin*

Take home messages

- In later-onset (‘milder’) cases - total fatty acid oxidation flux may be normal – need to measure individual enzyme activities or genetic studies
- Value of plasma acylcarnitine profile vs. blood spot acylcarnitine profile, use ratios!
- Most of the diagnosis is in the history!

Workshop Fatty acid oxidation defects

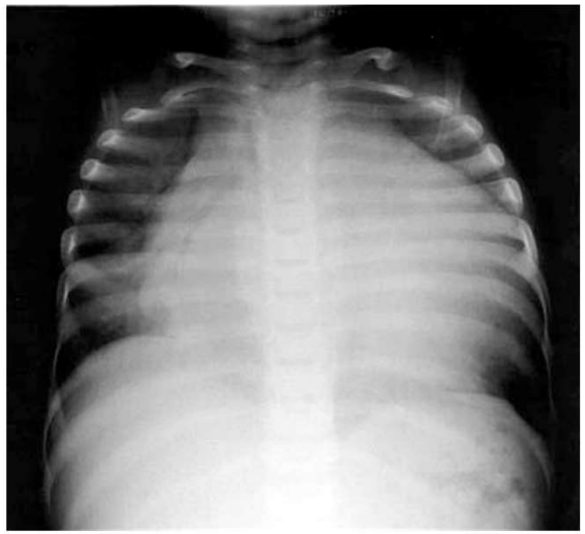
Case 2
A big heart

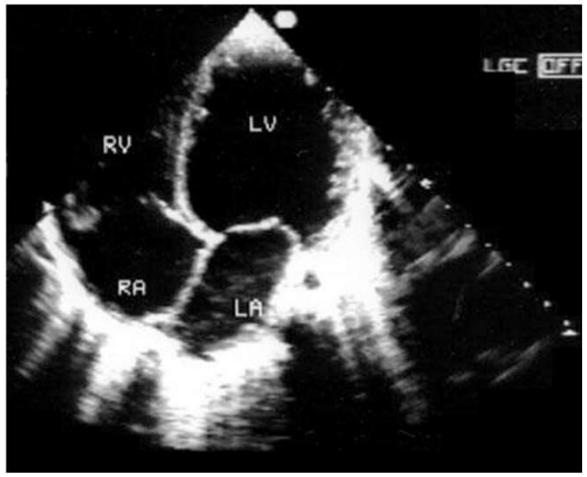
Clinical features

- Adrien, 4 year old boy
- 1st child of distantly consanguineous parents
- No perinatal problems
- Walked at 15 months but frequent falls
- Admitted with 3 months fatigue, anorexia, vomiting and weight loss
- On examination, tachypneic, quiet wheeze
- Tachycardia, low blood pressure
- Weak but normal reflexes
- Hepatomegaly, 2-3 cm below costal margin

Investigations

- Normal blood count & CRP
- CK 500 U/L (<200)
- ALT 100 U/L (<36), AST 180 U/L (<60)
- Normal blood glucose and ammonia
- Lactate 5 mmol/L (<2.0)
- Chest X-Ray
- Echocardiography





How can you put these findings together?

- Heart failure due to dilated cardiomyopathy
- Myopathy
- Hepatomegaly: right heart failure or storage

Questions

Which IEMs cause a dilated cardiomyopathy & myopathy?

- Primary carnitine deficiency (defect of OCTN2 transporter in plasma membrane)
- Mitochondrial defects (e.g. ACAD9 defect, Barth syndrome etc)
- Propionic acidaemia
- Lysosomal disorders (e.g. MPS I within 1st year)
- Other FAODs & Pompe disease → hypertrophic, maybe dilated when advanced

What is your immediate treatment?

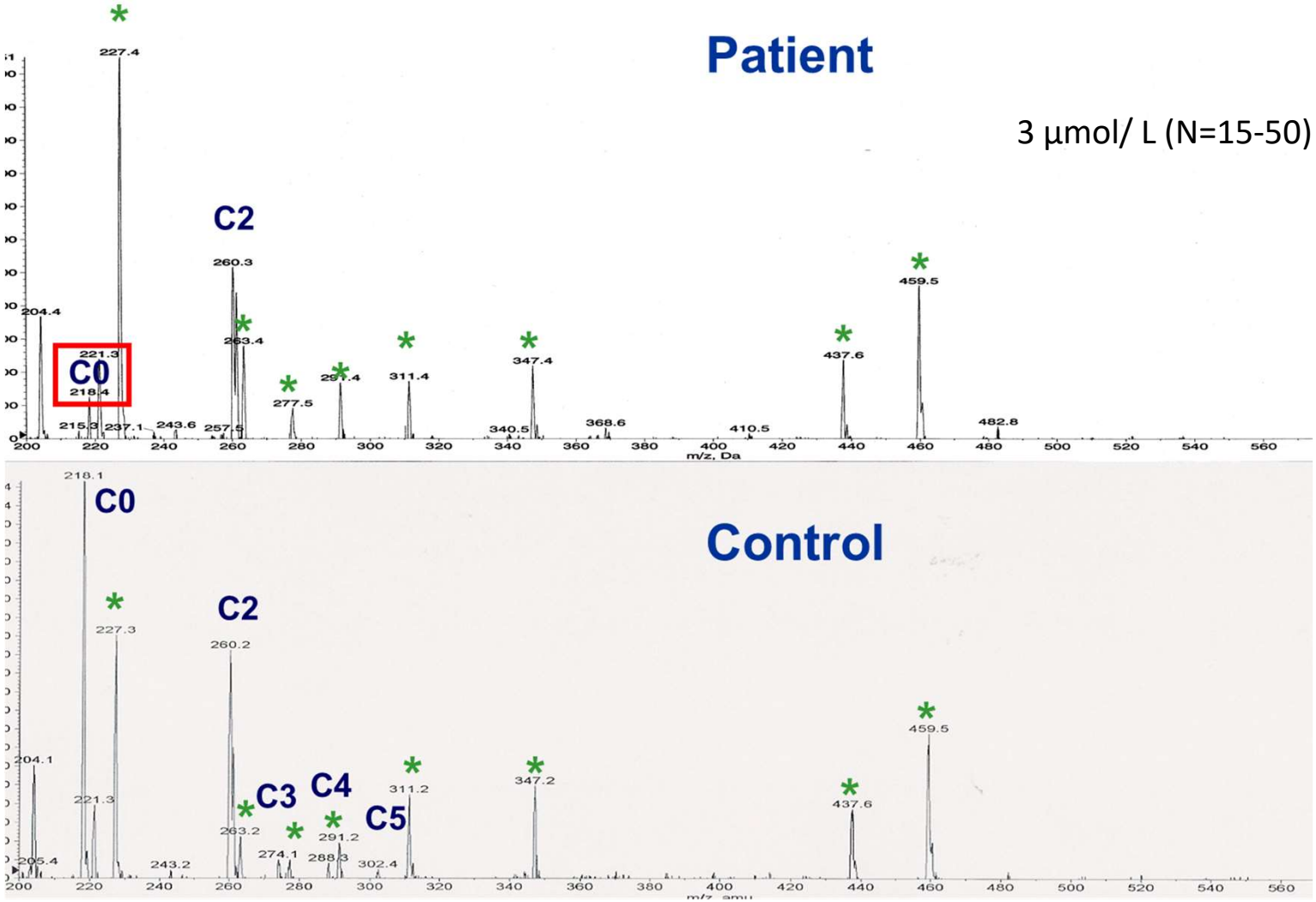
- L-carnitine: 100 mg/kg/day in 3 doses
- IV glucose infusion: 7 mg/kg/min
- No lipids
- Treatment of heart failure (inotropes, anti-congestives, diuretics, anti-coagulants?)
- Monitor ECG and blood glucose

Questions

What other investigations would you do?

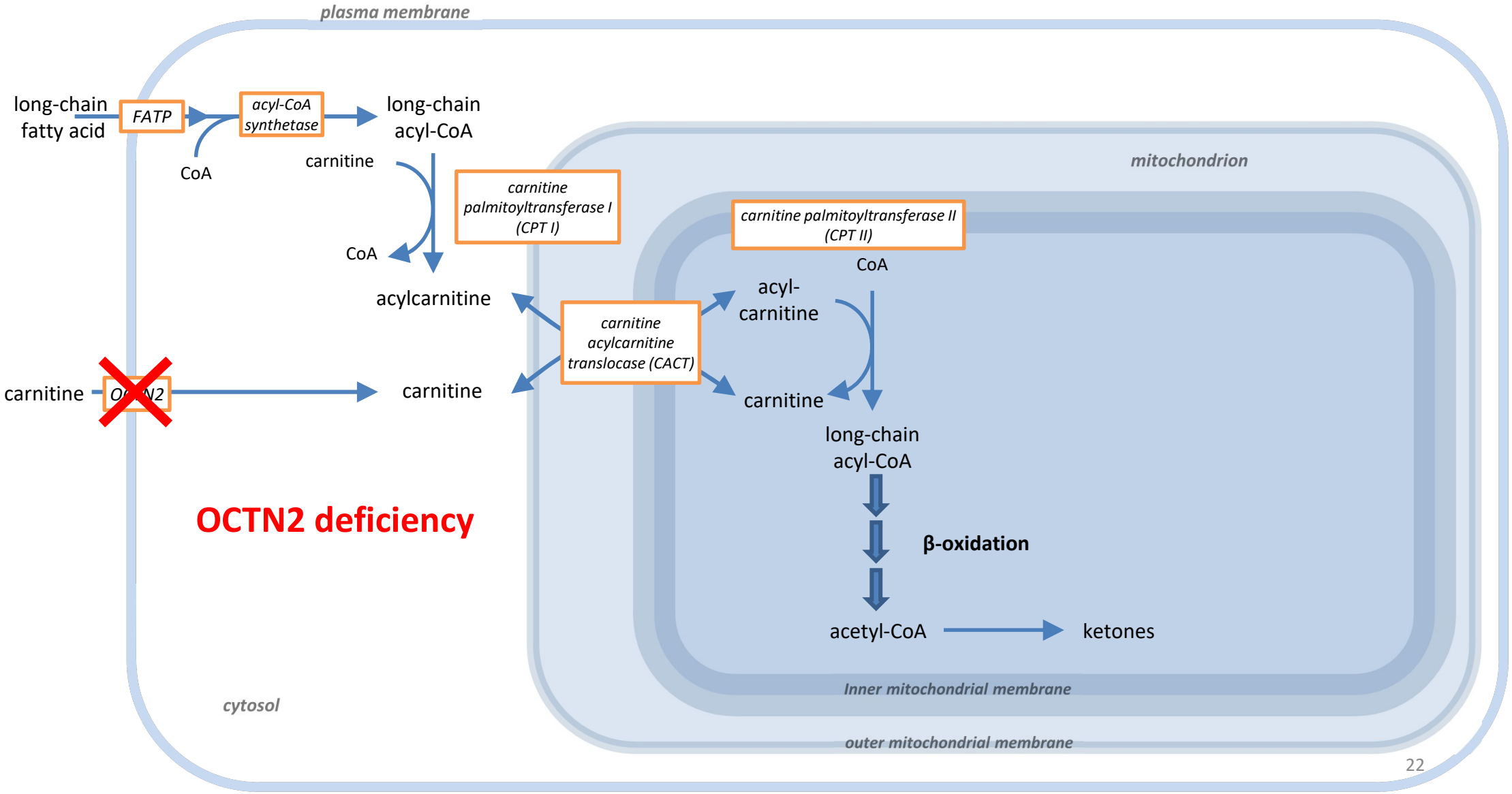
- Viral serology - negative
- Urine organic acids
  - Dicarboxylic aciduria out of proportion to low ketone body excretion
- Plasma acylcarnitine profile
  - Free & acylcarnitines all low, needs repeating when free carnitine higher
- Plasma free carnitine - 3 µmol/ L (normal 15-50)
- Simultaneous urinary carnitine (normal)
  - Fractional excretion of free carnitine 31% (normal <2%)
- Molecular analysis of *SLC22A5* (gene for OCTN2)
- If inconclusive: Fibroblast carnitine uptake assay

Acylcarnitines in plasma



3 µmol/ L (N=15-50)

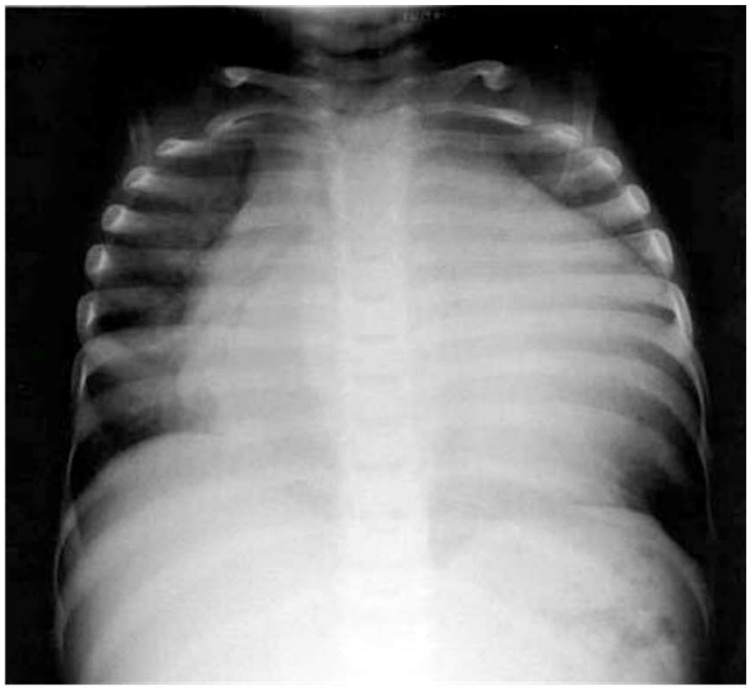
Mitochondrial fatty acid β-oxidation



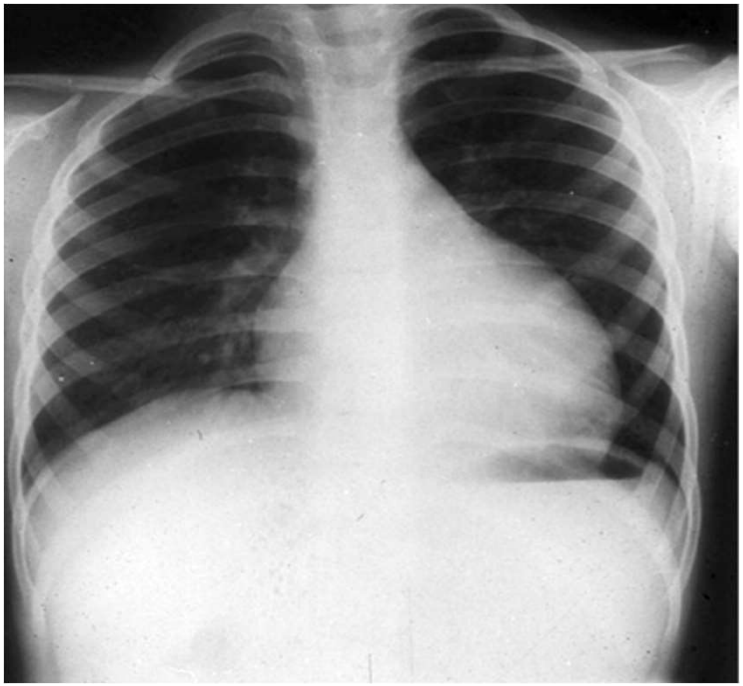
Outcome

After 4 weeks on L-carnitine:
Plasma free carnitine: 28 µmol/ L (normal 15-50)
Blood spot acylcarnitine profile normal

Before L-carnitine



After 4 weeks on L-carnitine



Carnitine Deficiency

- Plasma free concentration < normal
  - i.e. <15 µmol/L
- Transporter deficiency likely if free and total carnitine < 5 µmol/L
- Seldom symptoms if >10-20% normal
- In OCTN2 deficiency, symptoms more likely as intracellular concentration more abnormal than plasma

What are potential causes?

- Primary deficiency (OCTN2)
- Secondary deficiencies:
  - Inborn errors of Metabolism
    - Organic acidurias, FAODs, Mitochondrial defects
  - Fanconi syndrome
  - Drug-induced carnitine deficiency
    - Pivmecillinam, Valproate, Cyclosporine
  - Prematurity
  - Total Parenteral Nutrition
  - Hemodialysis

Adult slide

Messages

Primary carnitine (OCTN2 transporter) deficiency presentations:

- Cardiomyopathy usually aged 1-7 yrs
- Myopathy usually aged 1-7 yrs
- Fasting hypoglycaemia usually aged <2 yrs
- Arrhythmias as adults?
- Asymptomatic

Treatment: carnitine (100-400 mg/kg/d in 3 doses) can prevent all symptoms

Diagnosis: disproportionate carnitine excretion, molecular genetics, transporter assay (fibroblasts)

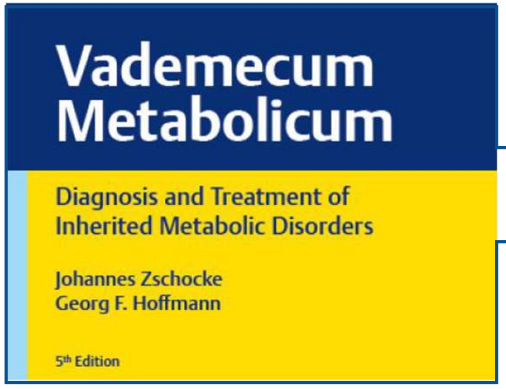
Repeat acylcarnitine profile after carnitine deficiency corrected

Workshop Fatty acid oxidation defects

Case 3
Post-mortem IMD diagnosis

Case: 20-month-old boy

- Previously fit and well
- One day history of lethargy, fever, vomiting
- Found unresponsive, resuscitation unsuccessful
- Body taken to local Emergency Department
- What samples might help identify a metabolic cause of death?



Sudden unexpected death PM investigations

Sample for DNA *absolutely essential!*

Basic metabolic tests

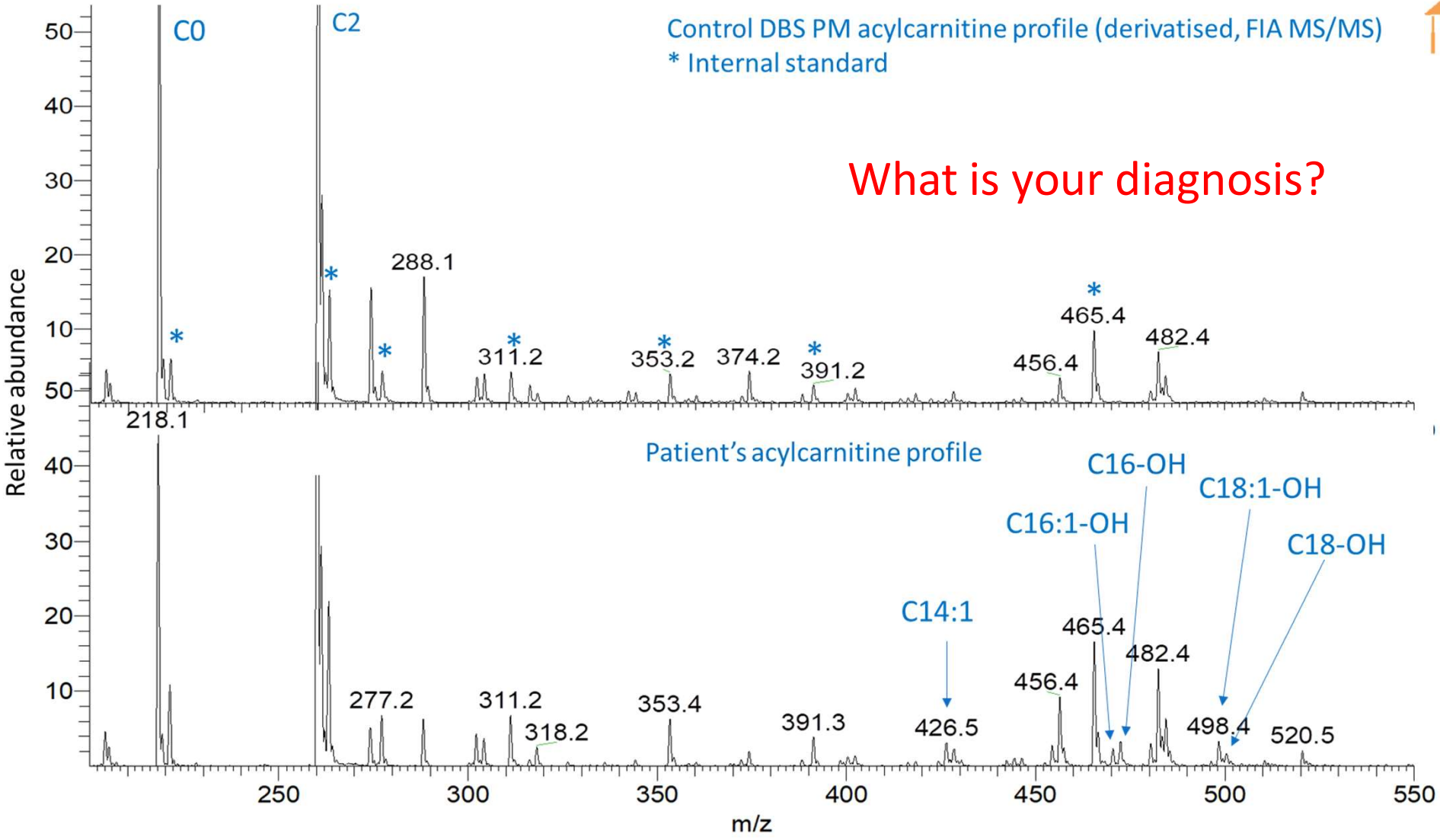
- Acylcarnitines from blood (and/or bile)
- Amino acids in plasma (and CSF?)
- Organic acids in urine (bladder often empty)
- Skin for fibroblast culture

Post-mortem (PM) laboratory results

- Microbiology
  - CSF - increased leukocytes (90% lymphocytes) and red blood cells
  - Blood culture - gram positive cocci
- Toxicology
  - Serum drug screen – therapeutic paracetamol, no other drugs detected

Cause of death: Meningitis
(reported before metabolic test results available)

- Metabolic
  - Plasma amino acids – general increase, no evidence of amino acid disorder
  - No urine for organic acids
  - Blood spot acylcarnitines



What is your diagnosis?

Diagnosis

- LCHAD or MTP deficiency
- Newborn screening blood spot retrieved & analysed (in UK no screening for FAODs except MCAD deficiency)
  - Increased long-chain OH-acylcarnitines
- Genetic testing
  - Homozygous variant *HADHA* c.1528G>C, p.E510Q
  - Consistent with LCHAD deficiency

PM DBS sample	Result (µmol/L)	Upper ref limit (PM values)
C16:1-OH	0.24 ▲	0.13
C16-OH	0.39 ▲	0.13
C18:1-OH	0.41 ▲	0.11
C18-OH	0.22 ▲	0.10

NBS DBS sample	Result (µmol/L)	Upper ref limit
C16:1-OH	✓ 0.06	0.11
C16-OH	✓ 0.13	0.13
C18:1-OH	✓ 0.05	0.11
C18-OH	✓ 0.07	0.10
(C16-OH+C18-OH +C18:1-OH)/C2	▲ 0.09	0.01

Mitochondrial Trifunctional Protein

α-subunit
HADHA

long-chain enoyl-CoA hydratase domain	long-chain 3-hydroxyacyl -CoA dehydrogenase domain

Prevalent mutation (c.1528G>C)

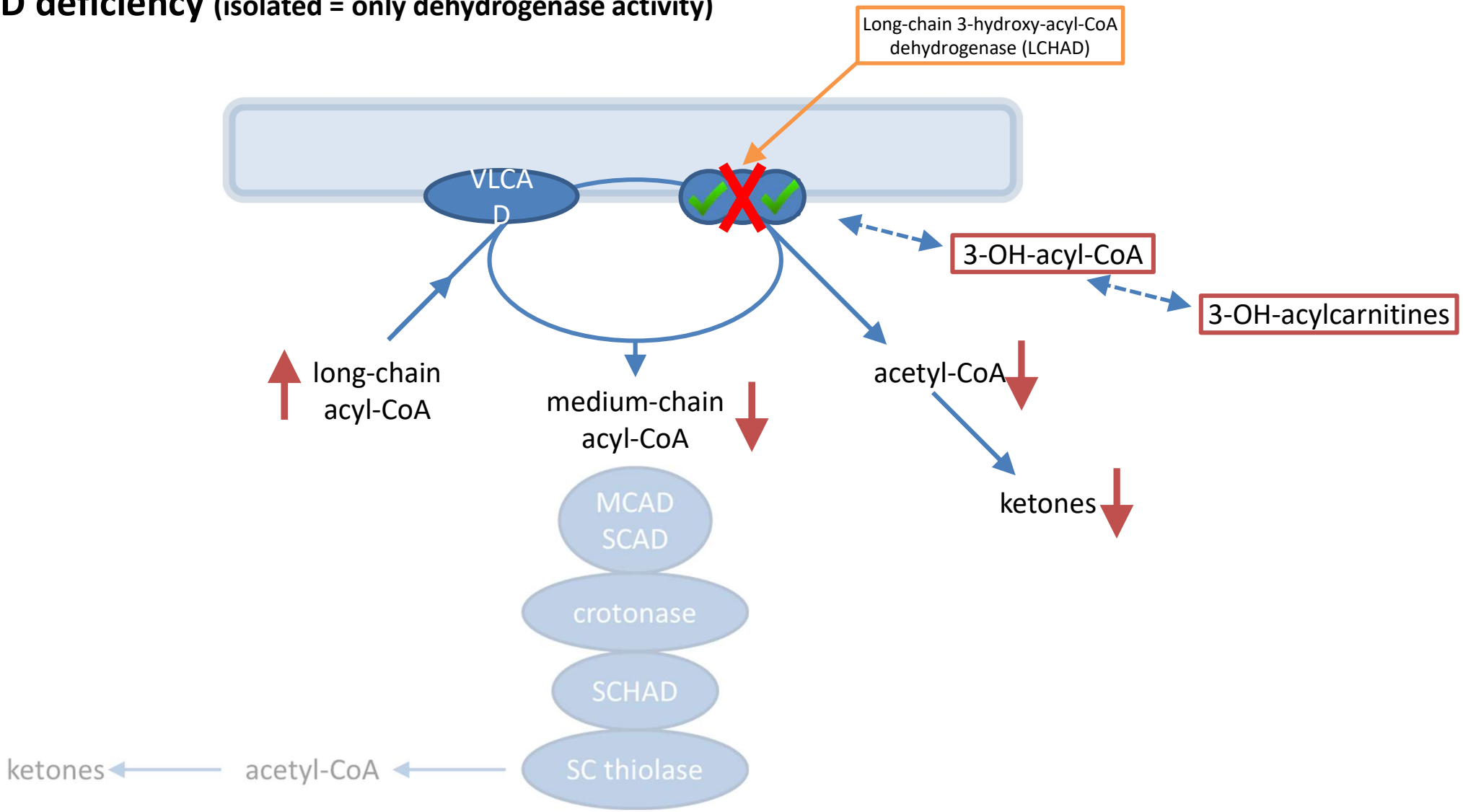
β-subunit
HADHB

long-chain 3-oxoacyl-CoA thiolase

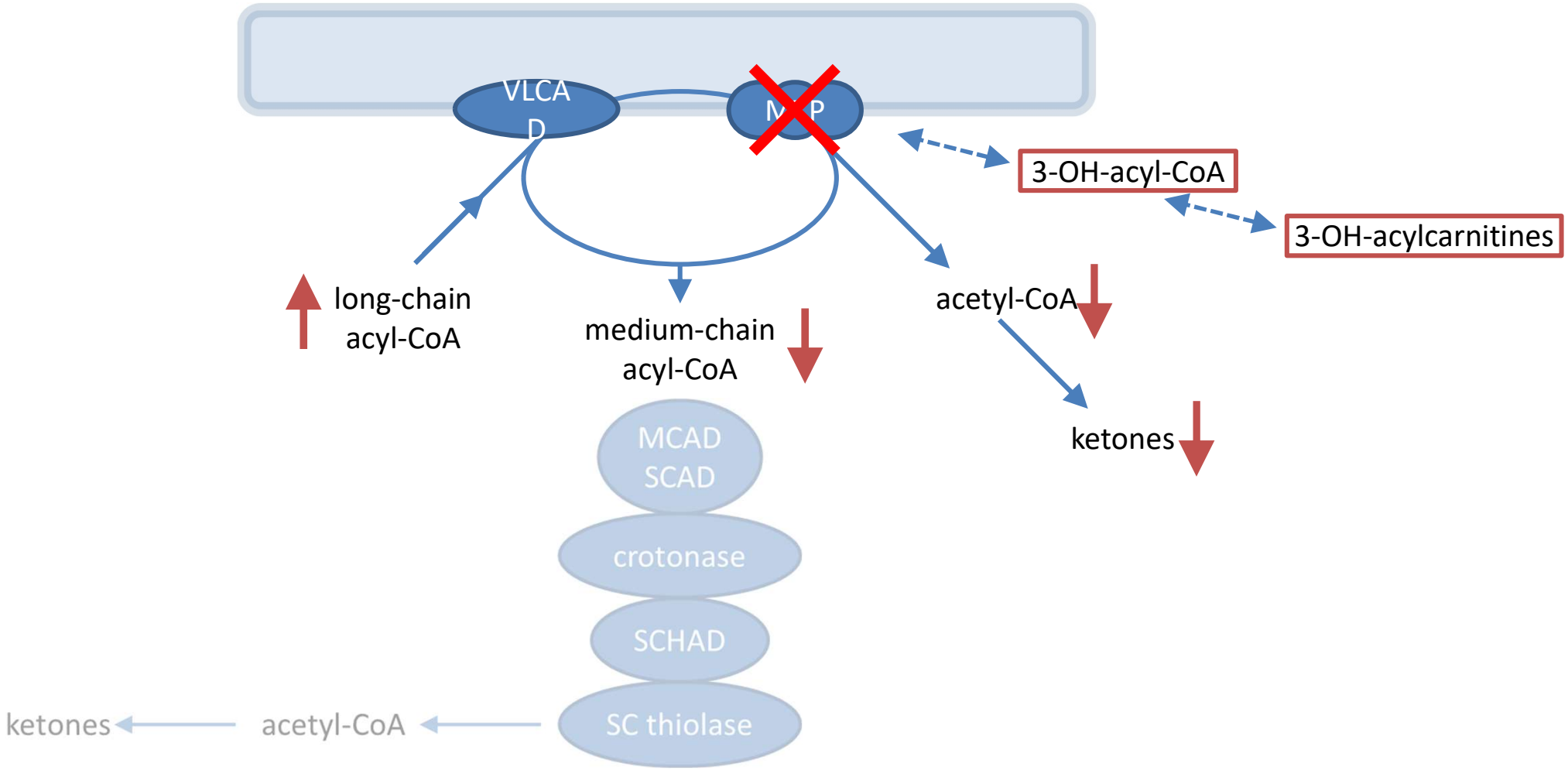
Isolated LCHAD deficiency: 90% c.1528G>C homozygotes

MTP deficiency (*HADHA* or *HADHB*): some severe, some mild cases

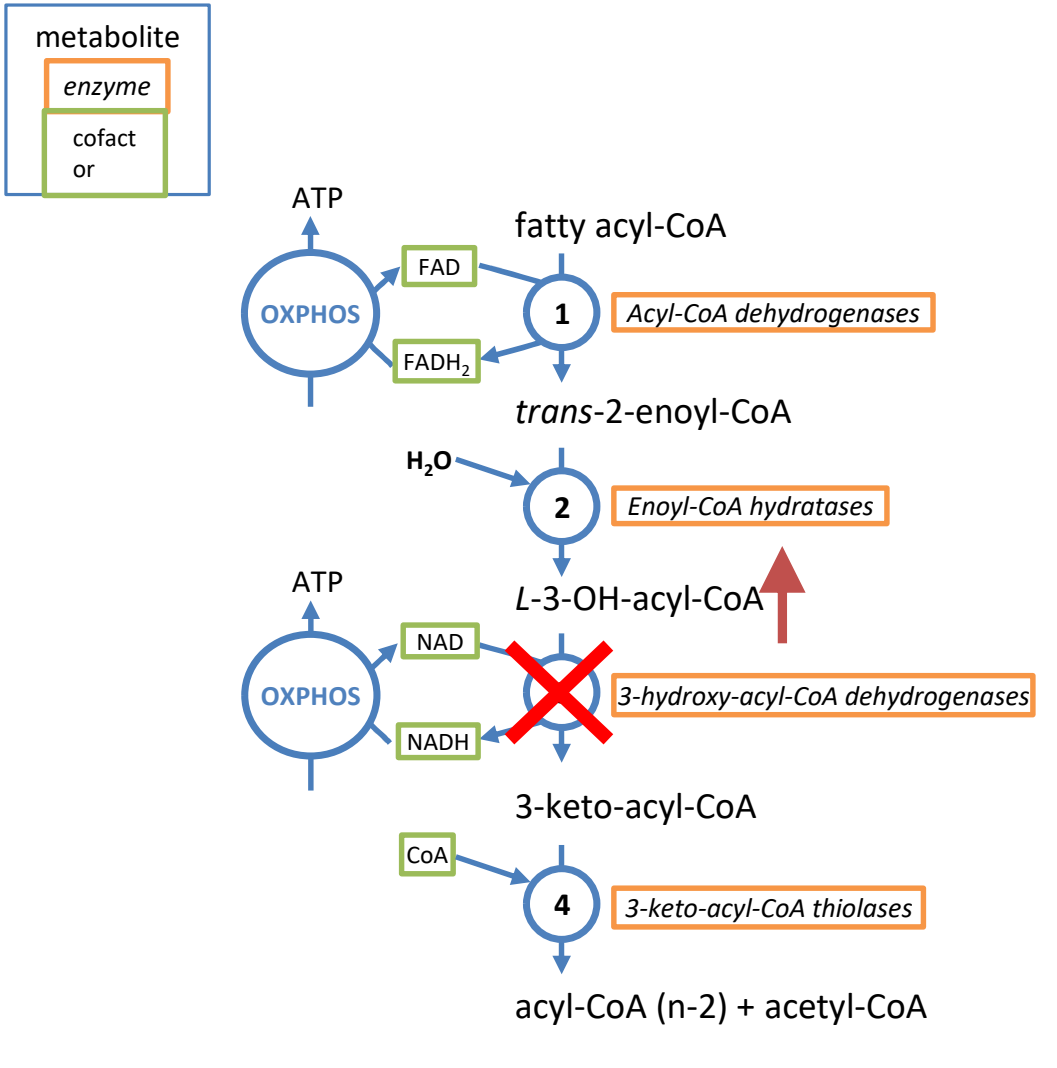
LCHAD deficiency (isolated = only dehydrogenase activity)

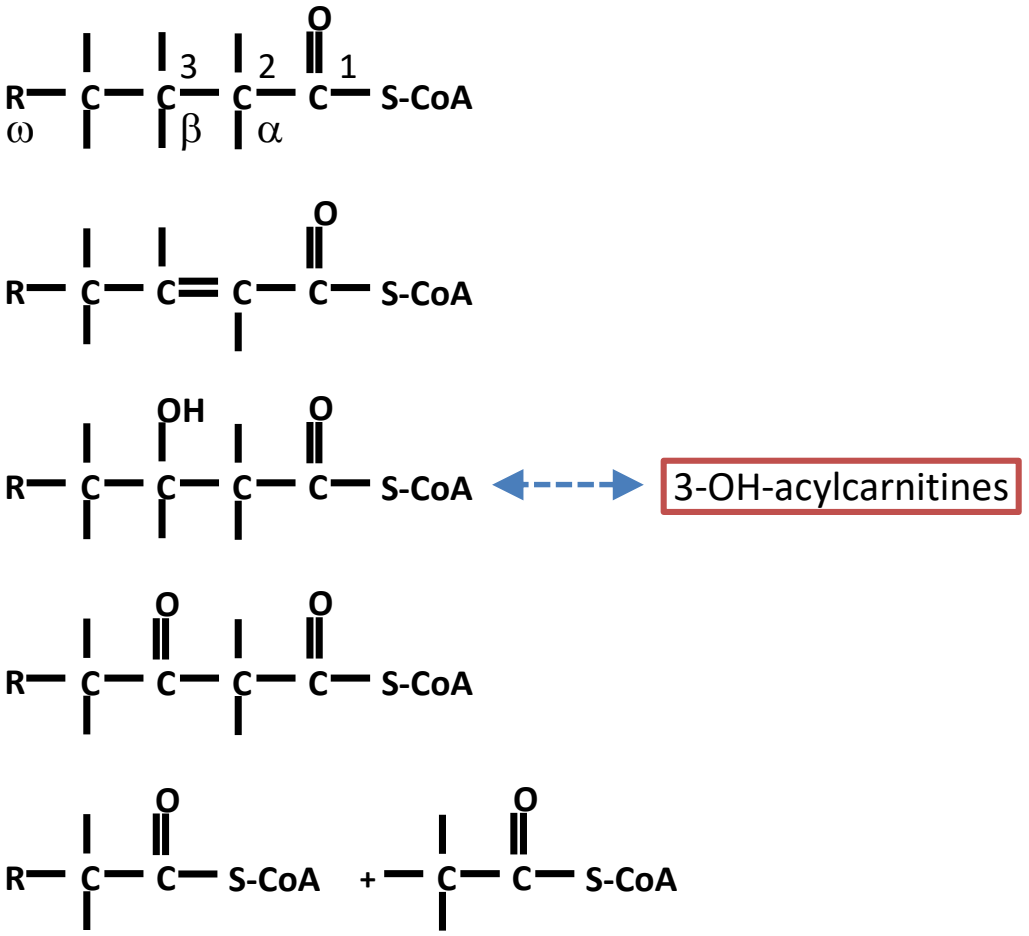


MTP deficiency (complete = all activities)

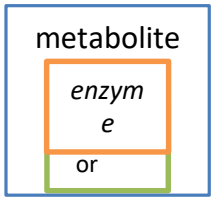


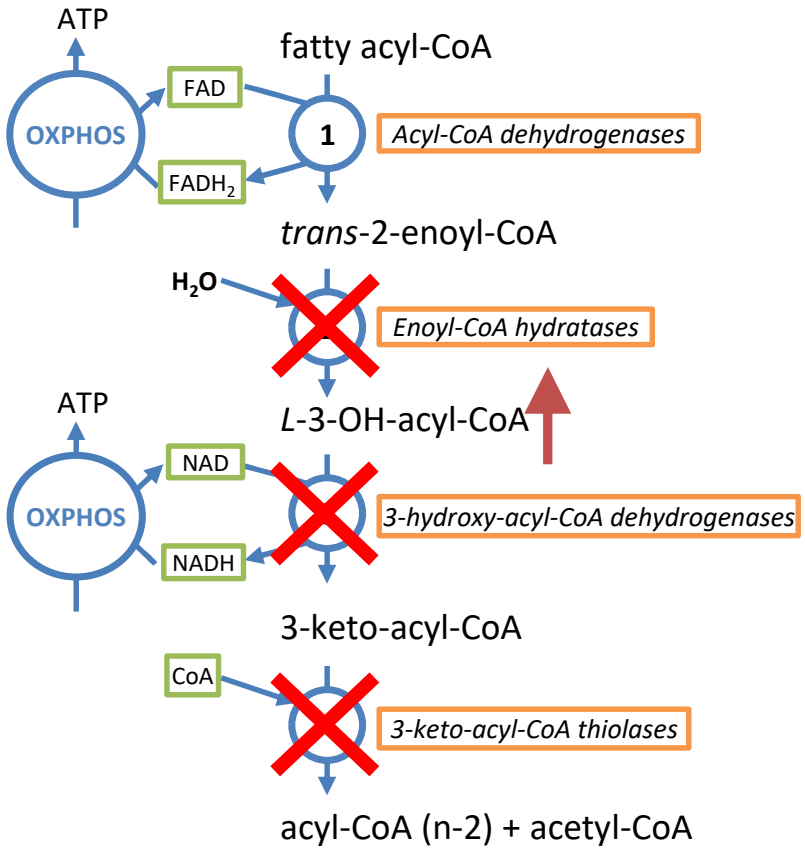
LCHAD deficiency

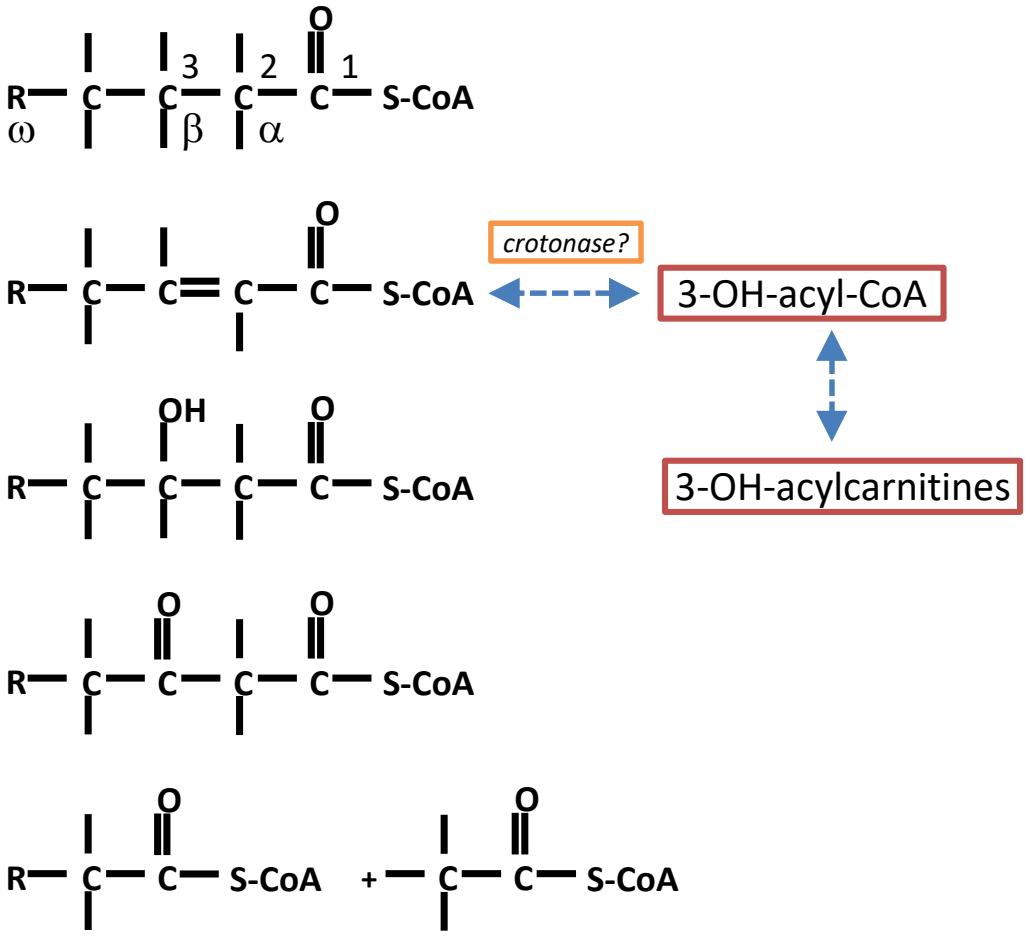




MTP deficiency







What are the clinical features of LCHAD/MTP deficiencies?

SSIEM ACADEMY 2023

Acute neonatal/infantile presentations

- Sudden unexpected death
- Acute illness in first few days or with minor infection later in the first 2 years
- Hypoketotic hypoglycaemia & lactic acidosis ± hyperammonaemia
- Cardiomyopathy
- Liver dysfunction (± cholestasis)

Later in life

- Rhabdomyolysis (at any age)
- Pigmentary retinopathy (childhood-onset, can be delayed by diet), cataracts
- Peripheral neuropathy (sometimes adult onset)

Heterozygous mothers

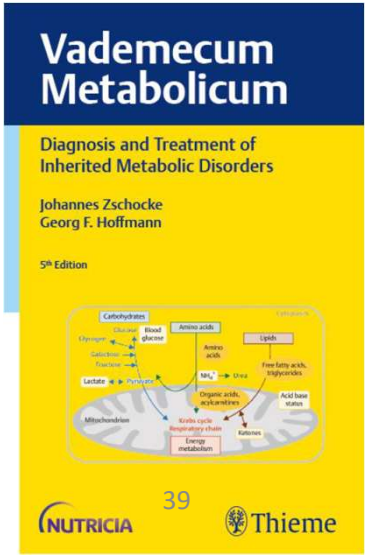
- may get HELLP or AFLP when carrying an affected fetus

How would you manage LCHAD deficiency?

- Emergency regimen during acute illness
- Avoid prolonged fasting
- Low long-chain fat diet, MCT supplementation
- Consider triheptanoin
- L-carnitine not usually recommended (OH-acylcarnitines cardiotoxic?), maybe in confirmed deficiency

Take home messages

- Fatty acid oxidation disorders are much the commonest metabolic cause of sudden unexpected death
- LCHAD and MTP deficiencies are usually easy to diagnose by acylcarnitine analysis but interpretation of post-mortem acylcarnitines can be tricky
- If a child dies of an unknown cause, it is essential to collect samples for metabolic & genetic tests
- A protocol is found in the Vademecum Metabolicum



Workshop Fatty acid oxidations defects

Case 4
Severe hypoglycemia and hepatomegaly

History & examination

- 1st child of non-consanguineous parents
- Healthy till gastroenteritis aged 16 months
- Admitted unconscious
- Hypoglycaemia (1.0 mmol/L)
- Severe hepatomegaly (7 cm below ribs)

Treated with intravenous glucose infusion

- Rapidly regained consciousness
- Hepatomegaly gradually improved

Investigations

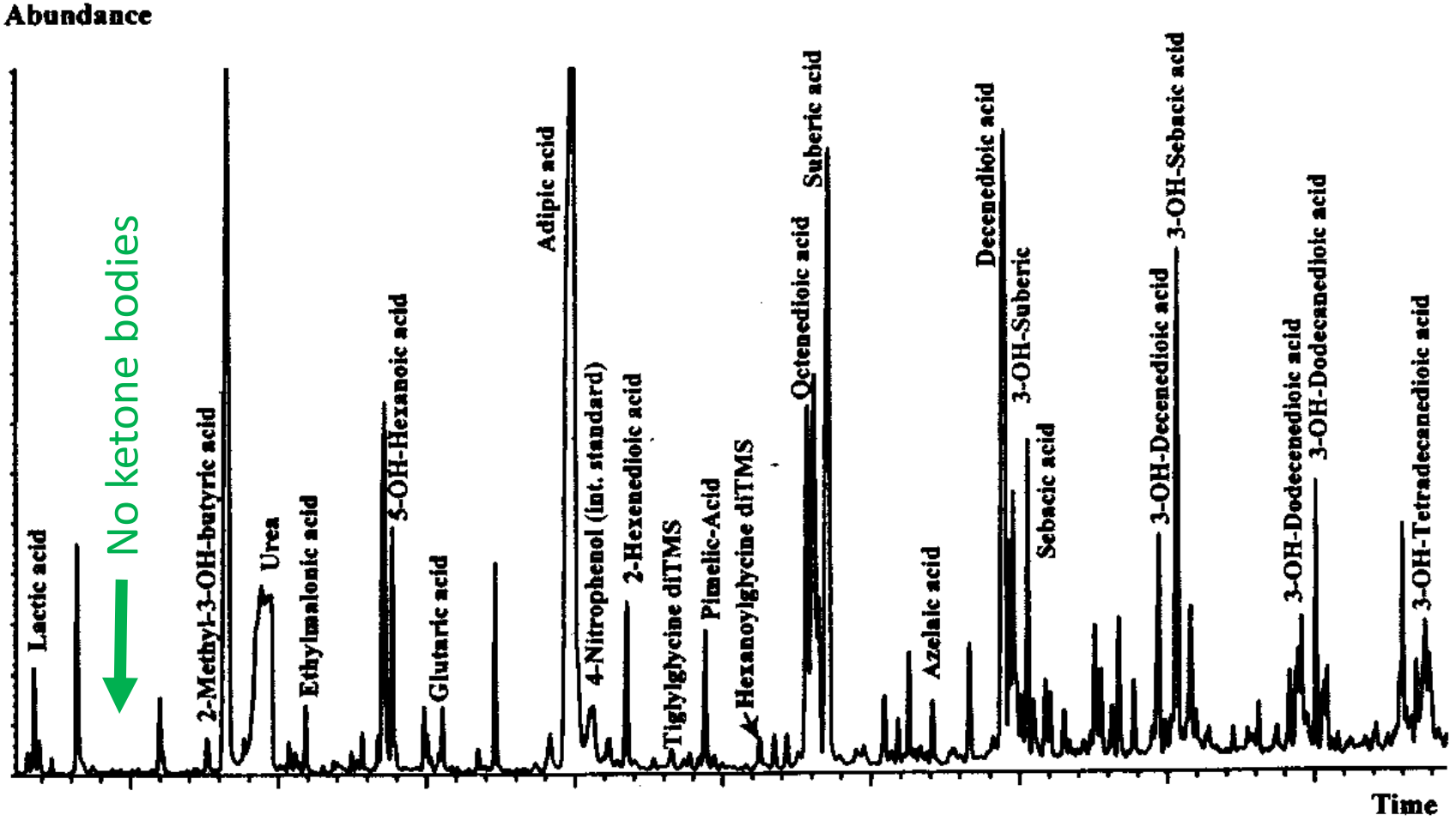
- Routine haematology & biochemistry normal
- Ammonia, lactate, urate & creatine kinase normal
- Alanine aminotransaminase 590 U/L (controls <45)
- Ultrasound: hepatomegaly, increased echogenicity

What other investigations would you do?

- DBS acylcarnitines: increased acetylcarnitine (C2), no other abnormality, C4OH not raised
- Echocardiography normal

What does the urine organic acids trace show?

Hypoketotic dicarboxylic and 3-hydroxydicarboxylic aciduria



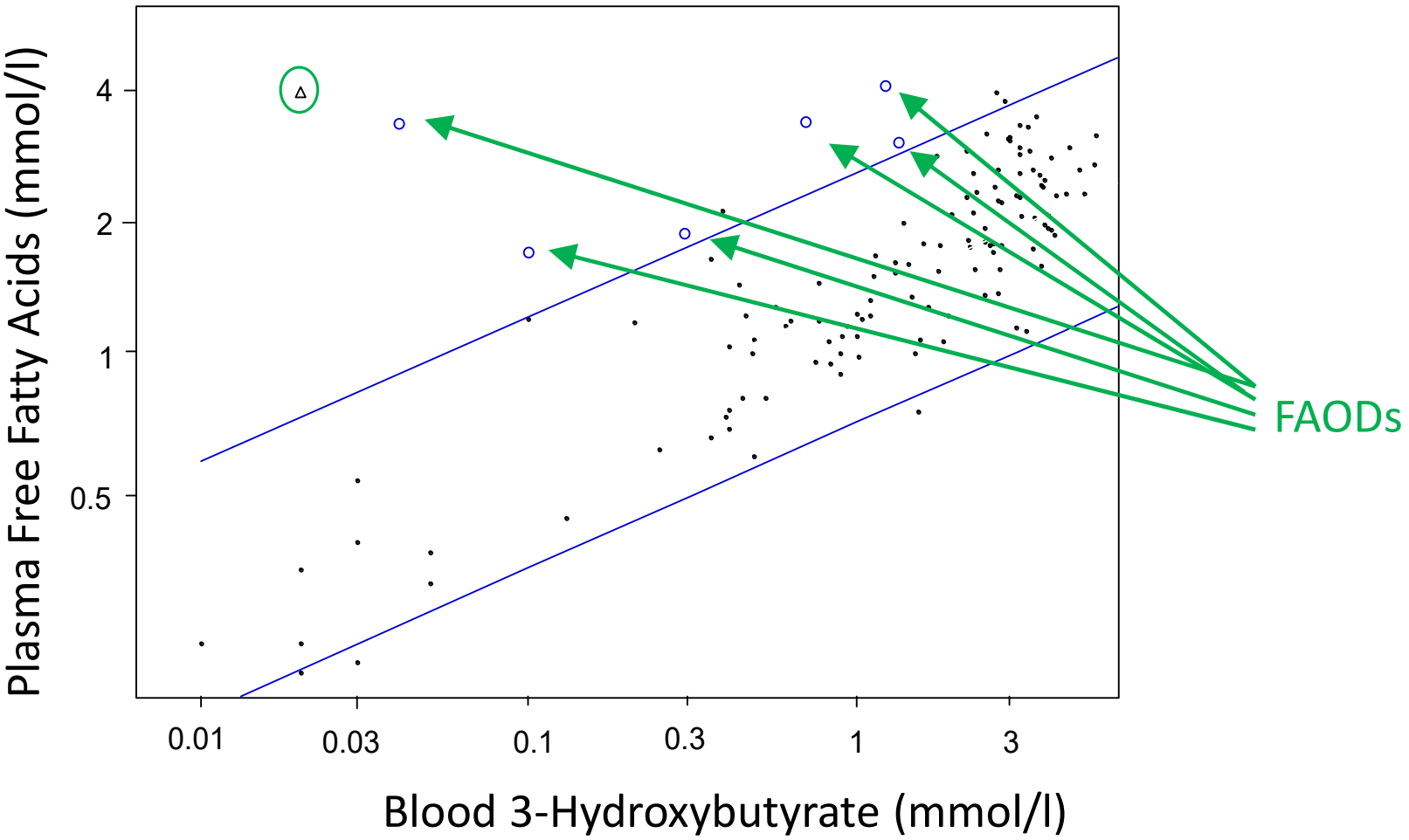
How would you investigate this further?

- Genetic tests were not readily available in 1998!
- Tritium release assay of fatty acid oxidation flux in fibroblasts: Normal with Oleate, Myristate & Palmitate substrates
- Fasting test

Duration (hours)	13	15	17	18
Glucose (mmol/L)	4.1	3.8	2.9	2.3
Free fatty acids (mmol/L)	2.4	2.5	3.3	4.0
3-hydroxybutyrate (mmol/L)	0.03	0.05	0.05	0.02

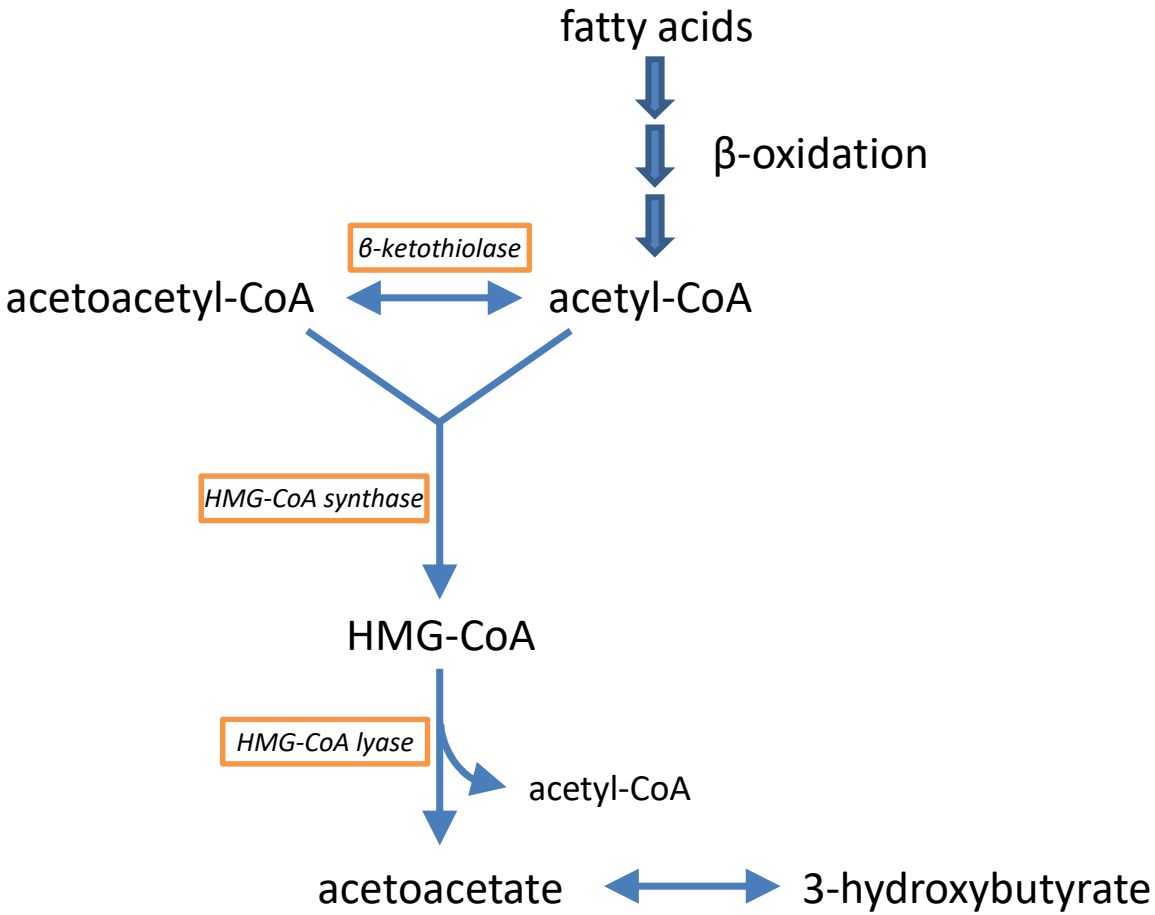
What does the fasting test show?

Fasting test

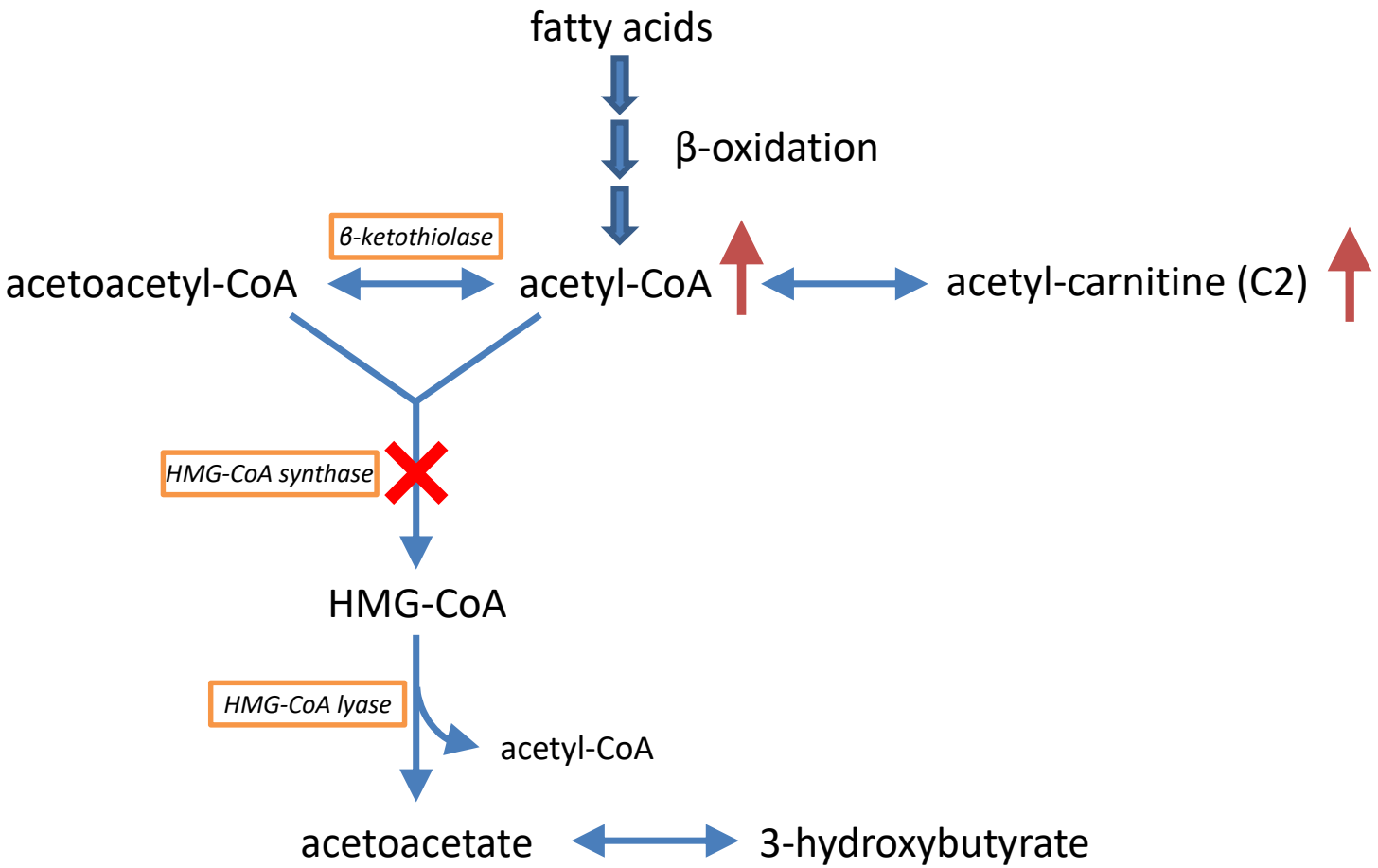


What might cause this picture?

ketogenesis



HMG-CoA synthase deficiency



How would you confirm the diagnosis?

- Western blotting for mitochondrial HMG-CoA synthase - no immunoreactive material in liver biopsy homogenate
- Total HMG-CoA synthase activity in liver 50% control values – probably due to cytoplasmic isoenzyme (involved in cholesterol synthesis)
- Compound heterozygous *HMGCS2* variants c.1270C>T (p.Arg424X) & deletion of exons 1&2

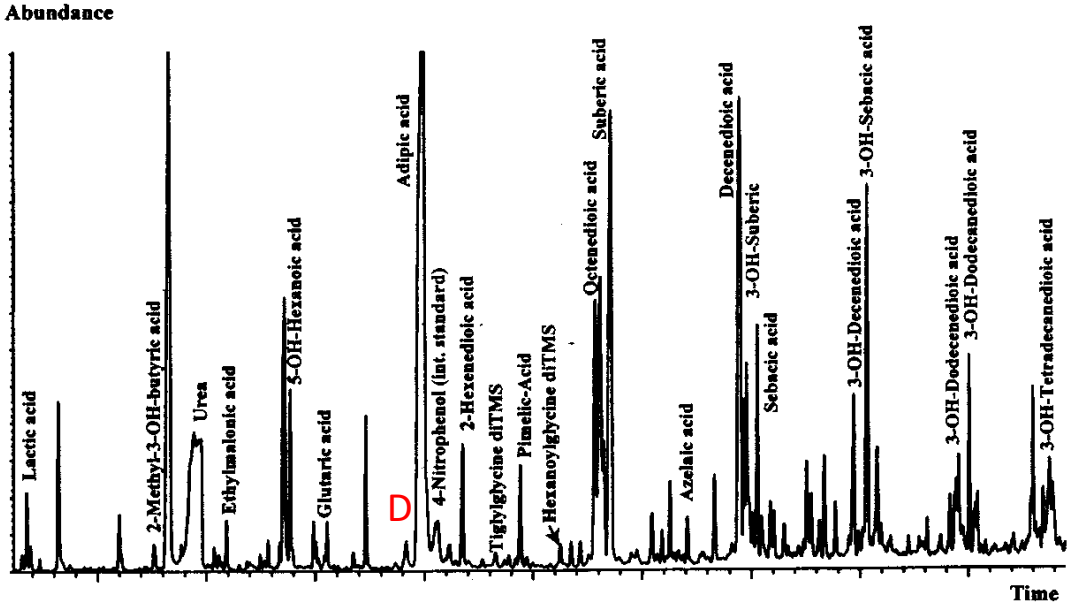
Management

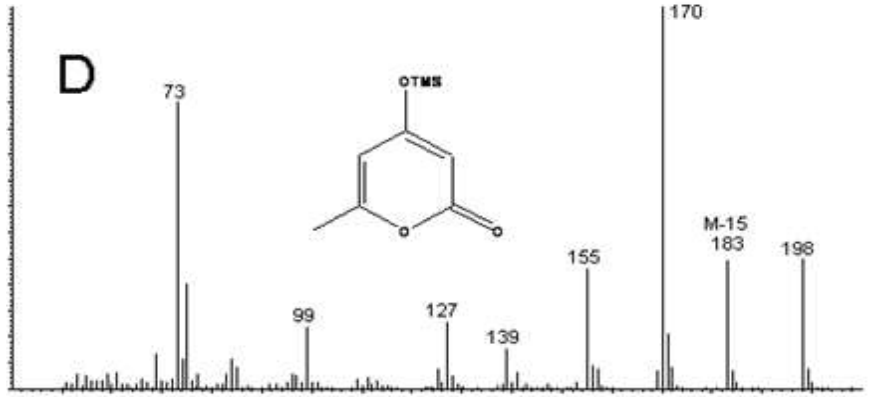
- Advised to maintain high glucose intake during infections & avoid prolonged fasting
- Normal development, no further metabolic problems

Morris et al, 1998, Ped Res 44:392-6

Messages

- Consider HMG-CoA synthase deficiency if the clinical picture suggests a FAOD but this isn't confirmed
- Acylcarnitines during acute decompensations: increased C2/C0 ratio despite hypoketosis
- Organic acid profile is relatively specific, especially 4-hydroxy-6-methyl-2-pyrone (eluted before adipic acid)
- Diagnosis now confirmed by gene sequencing

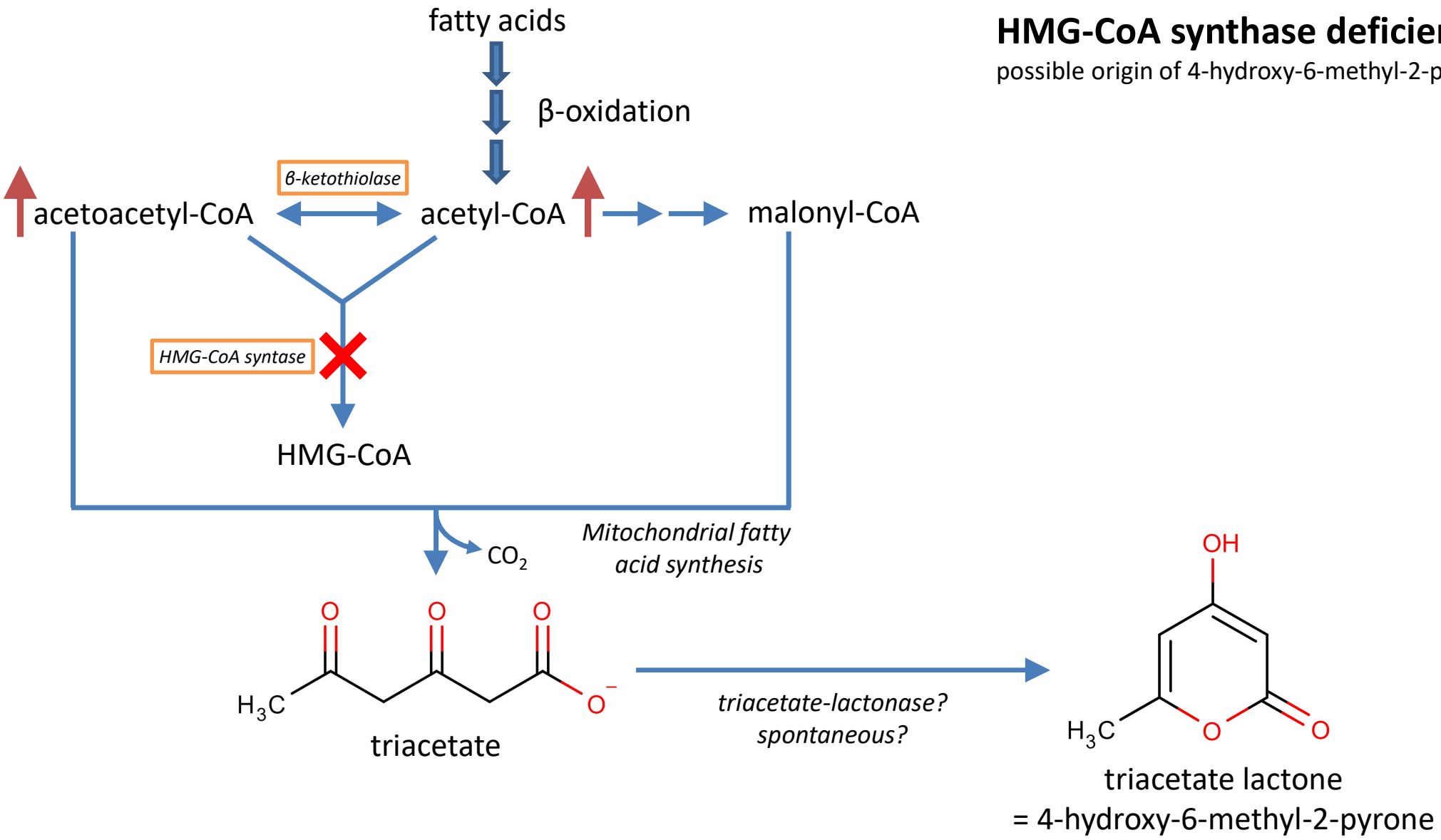




Pitt et al, (2015) JIMD 38:459-466

HMG-CoA synthase deficiency

possible origin of 4-hydroxy-6-methyl-2-pyrone



Workshop Fatty acid oxidation defects

Case 5
A 21 year old with fatigue

21 year old female

At university

Low mood and anxiety – started on anti-depressant medication

Leg fatigue on exercising, improved with rest

Gradually progressive over 2 years

Symptoms variable – thought to relate to her mood

Fall in shower, unable to get up, brought by ambulance to hospital

21 year old female

On admission:

- Metabolic acidosis: pH 6.85, HCO_3 2 mmol/L, lactate 3.5 mmol/L
- Ketosis
- Raised CK > 30,000 IU/L

Fall in consciousness
Intubated and ventilated for 3 days in Intensive Care Unit, haemofiltration
Admitted for 2 weeks – and made a full recovery to baseline

Provisional diagnosis: Starvation ketosis on the background of a mood disorder and possible conversion disorder (possibility of a metabolic myopathy also considered)

21 year old female

12 months later:

Re-admitted to hospital for investigation with weakness and difficulty mobilising

Progressive muscle weakness

Difficulty in swallowing and breathing

Metabolic acidosis and hyperammonemia – ammonia 121 µmol/L (RR: <35)

Intubated, ventilated, required tracheostomy & haemofiltration

How would you investigate?

21 year old female

Acylcarnitine profile

- Total carnitine — 14 µmol/L (26-62)
- Free carnitine — 10 µmol/L (22-50)
- Acylcarnitines — 4 µmol/L (4-12).
  Increased C8 and C10, C10>C8, C10:1 normal.

Urine organic acid profile

- Increased lactate.
- Heavy ketonuria (3-hydroxybutyric acid and acetoacetic acid).
- Significant dicarboxylic aciduria.
- ↑ ↑ ↑ hexanedioic acid.
- ↑ ↑ 2-oxoisocaproic acid and 2-oxo-3-methylvaleric acid.
- ↑ 3-hydroxyhexanedioic and octenedioic acids.

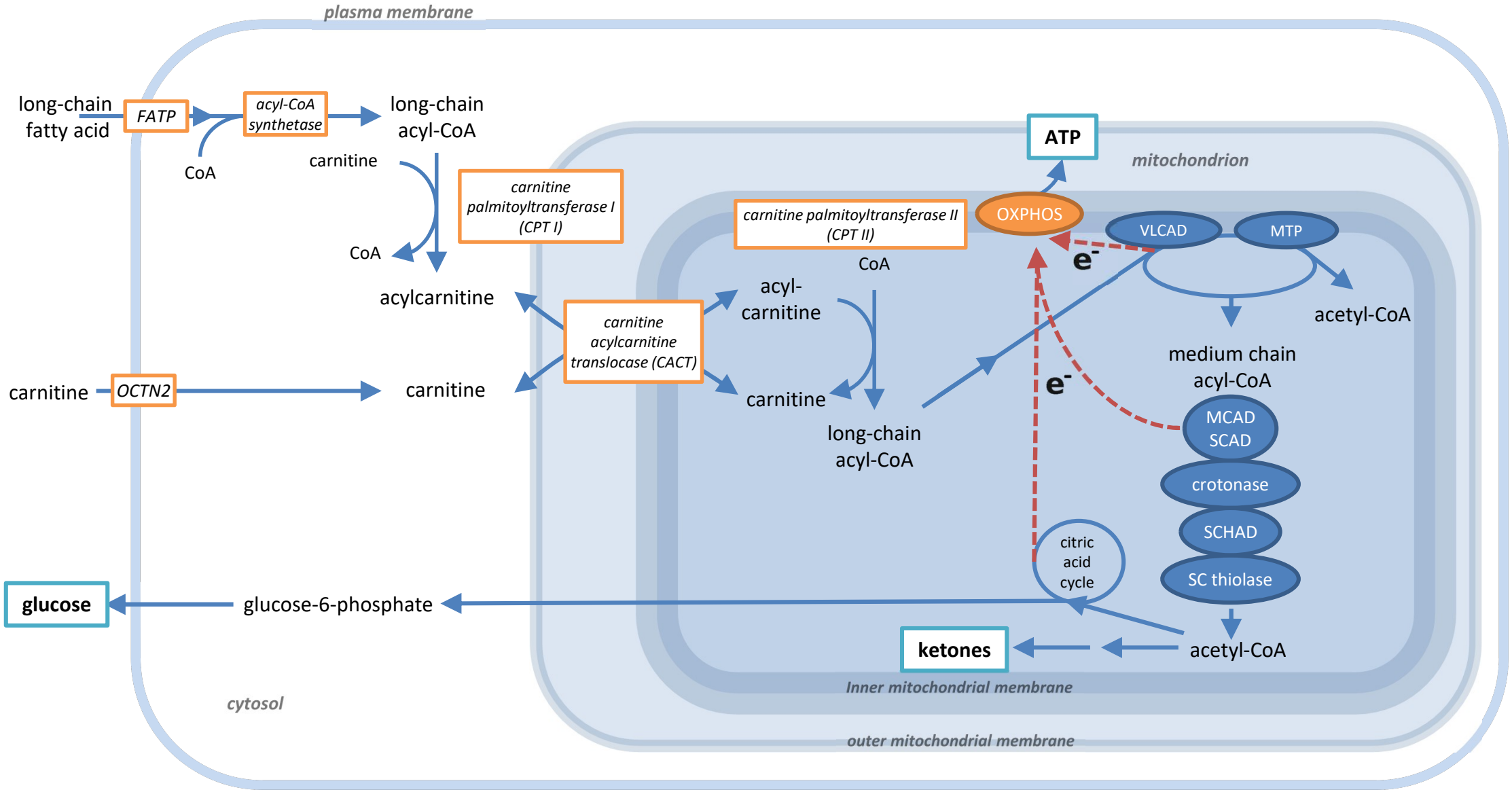
21 year old female

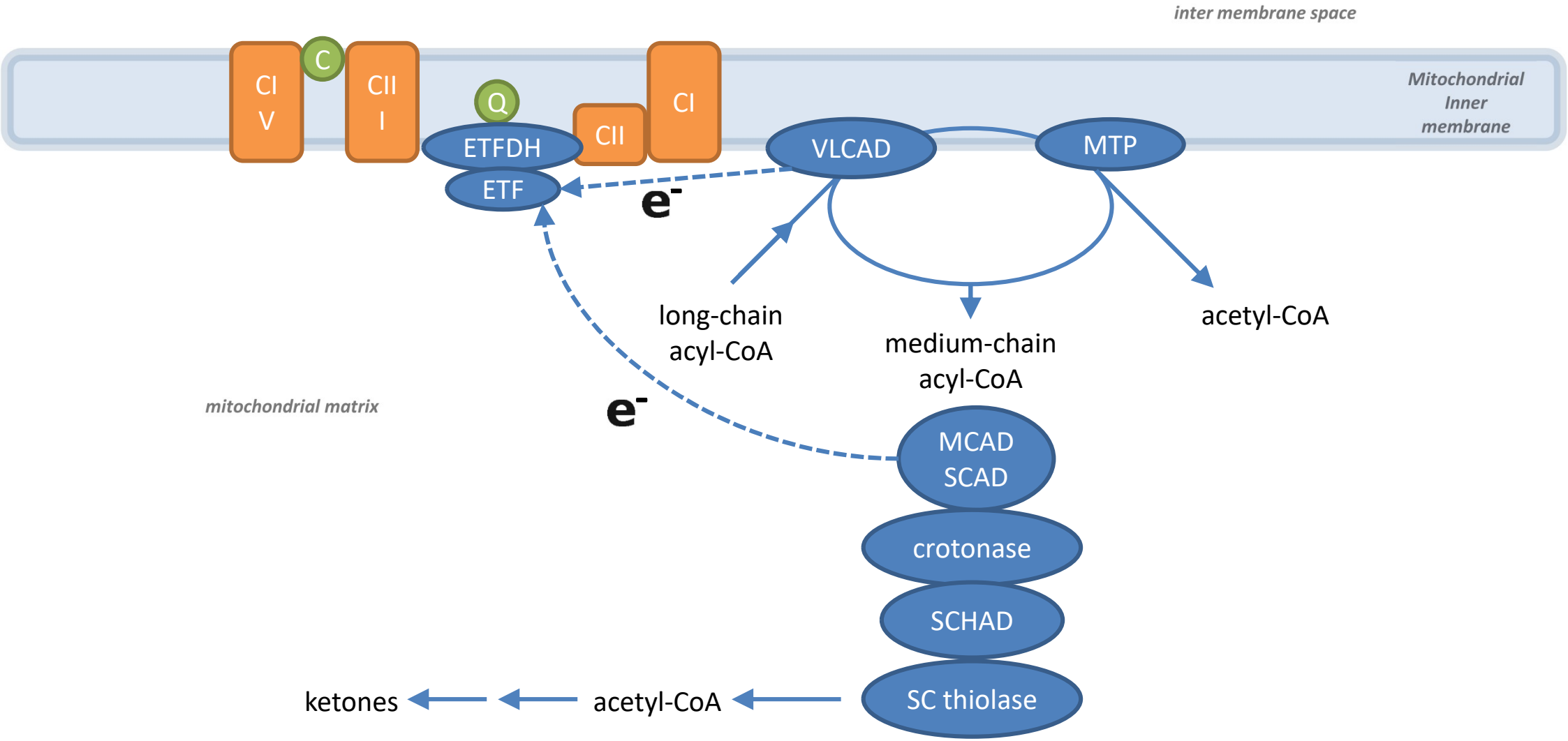
Genetic analysis

Heterozygous c.[51dup];[=], p.[(Ala18fs)];[9=0] in *ETFDH* gene.

Frameshift variant – known pathogenic.

Mitochondrial fatty acid β-oxidation




inter membrane space
Mitochondrial Inner membrane
CI V
C
CII I
Q
ETFDH
ETF
CII
CI
VLCAD
MTP
e-
long-chain acyl-CoA
medium-chain acyl-CoA
acetyl-CoA
mitochondrial matrix
e-
MCAD SCAD
crotonase
SCHAD
SC thiolase
ketones
acetyl-CoA

21 year old female

What might you expect fatty acid oxidation studies to show?

Tritium release assay of beta-oxidation of fatty acids

	Myristate (% of controls)	Palmitate (% of controls)	Oleate (% of controls)
@37C	160	154	171
@41C	164	175	187

What treatment would you advise?

Avoid / limit precipitants – fasting, fever / infection, prolonged exercise, anaesthesia

Trial of riboflavin (100 mg twice daily in this case)

Give an emergency regimen (may include L-carnitine)

Progress

Rehabilitation for 2 months as inpatient

Home with lower limb splints and a crutch to mobilise

Now: Mobilises independently,

Significant impact on mental health – also improved

No further hospital admissions or acute decompensation

Adults with MADD

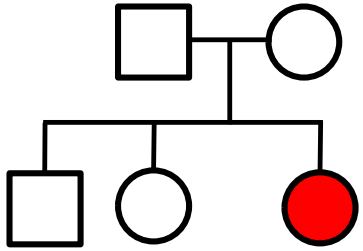
Age at symptom onset	17 years	21 years	Unclear	Adulthood	58 years
Age at diagnosis	18 years	24 years	25 years	57 years	64 years
Features at baseline	Cramps and myalgia on exertion. Mild proximal weakness	Exercise intolerance Progressive weakness	Exercise intolerance Myalgia	Myalgia	Intermittent profound muscle weakness
Features of decompensation	Rhabdomyolysis Encephalopathy	Rhabdomyolysis Encephalopathy Weakness	Myalgia Vomiting Diarrhoea		Weakness
Plasma acylcarnitines	Increased medium and long chain species (esp. C8-10)	Increased medium and long chain species	(Feb 17) Abnormally elevated C8 (0.79, ref. <0.22) and C10 (1.4, ref. <0.3). Normal free carnitine.	Raised C8 and C10 carnitines but with C10>C8, C10:1 normal. Elevated C12, C14:1 and C14.	Increased C6-C16 acylcarnitines
Genetic testing	Hetero. ETFDH c.51dup, p.(Ala18fs)	Hetero. ETFDH c.51dup, p.(Ala18fs)	Hetero. ETFDH c.135G>C, p.(Val451Leu)	Hetero. ETFDH c.135G>C, p.(Val451Leu)	Hetero. ETFDH c.51dup, p.(Ala18fs)
Clinical response to riboflavin	Good	Good	Good	Good	Good

Paediatric MADD (1)

- *Female, term delivery after uneventful pregnancy*
- *Day 1: Breastfeeding, discharged home*
- ***Day 2: Rapid breathing, poor feeding, slept 8 hours***
  - *Found hypothermic → cardiopulmonary arrest → resuscitation*

  - *Blood glucose 0.5 mmol/L*
  - *Lactate 9.8 mmol/L*
  - *pH 7.01, pCO2 5.4 kPa, HCO_3 14.5 mmol/L, BE -12 mmol/L*
  - *Ammonia 170 µmol/L*
  - *Deranged liver function tests*
  - *Urine: no ketones*

- *Echocardiogram normal*

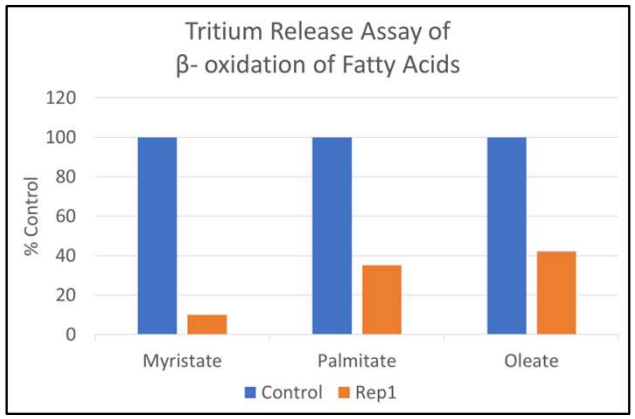


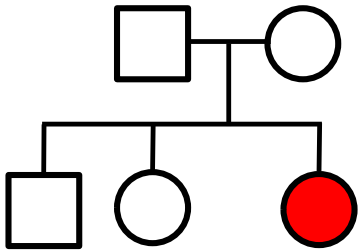
Paediatric MADD (1)

Acyclcarnitine Species	Umol/L	Ref range
Free Carnitine	**39**	28.5-109
C2 (acetyl)	**15.2**	0-50.3
C3 (propionyl)	**0.56**	0-1.27
C4 (Butyryl)	**3.83** ↑↑	0-0.72
C5 (Isovaleryl)	**2.98** ↑↑	0-1.2
C6 (Hexanoyl)	**1.04** ↑↑	0-0.48
C8 (Octanoyl)	**0.91** ↑↑	0-0.72
C5-DC (Glutaryl)	**0.17**↑↑	
C10 (Decanoyl)	**1.06**↑	
C14:1 (Tetradecenyl)	**1.42**↑	0-0.55
C14 (Tetradecanoyl)	**2.17**↑↑↑	
C12 (Dodecanoyl)	**1.23**↑↑	
C16-OH (Hydroxyhexadecanoyl)	**0.18**↑	
C16 (Palmitoyl)	**4.8**	0-8.43

Urine organic acids

- Ketones negative
- 2-hydroxyglutarate 409umol/mmol Creat
- Glutarate 155 umol/mmol Creat
- Hexanoylglycine 52 umol/mmol Creat
- Mildly raised adipte, suberylglycine, isobutyrylglycine, butyrylglycine, isovalerylglycine, 2 methylbutyrylglycine





ETFA & *ETFB*: no mutation
ETFDH: Exon 4 missense mutation & Intron 12 variant affecting donor splice site

MADD not biochemically responsive to riboflavin

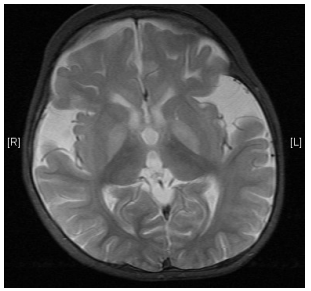
Paediatric MADD (1)

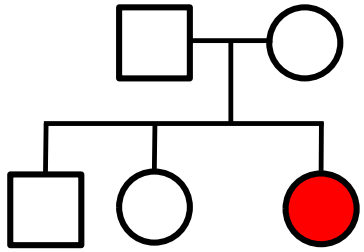
***Progress** (upto 13 years)*

- *Recurrent decompensation episodes*
- *Profound **skeletal myopathy** - wheelchair*
- *Chronic **hypoventilation** – nocturnal non-invasive ventilation*
- *Recurrent **rhabdomyolysis***
- *Chronic recurrent **pancreatitis** requiring pancreatectomy → Secondary diabetes*
- *Osteoporosis, pathological vertebral fractures*
- *Renal tubular dysfunction*
- *No significant cardiomyopathy*
- *Good cognitive development*

Treatment

- *Diet: controlled fat diet*
- *Emergency regimen glucose polymer*
- *Riboflavin*
- *Sodium DL-3-hydroxybutyrate 5x per day*

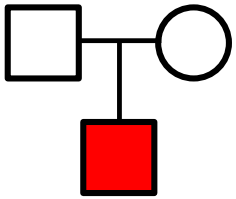




Paediatric MADD (2)

- *Male, term delivery*
- *Breastfed initially, formula feed introduced after 1 week*
- ***Routine day 5 newborn screening:** raised C8 (octanoyl) but normal C8/C10 ratio*

- *Acylcarnitine profile (newborn screening card): suggestive of MADD*
- *Acylcarnitine profile (day 12): normal*
- *Urine organic acids (day 12): normal*
- *ETFA, ETFB, ETFDH: no variants*



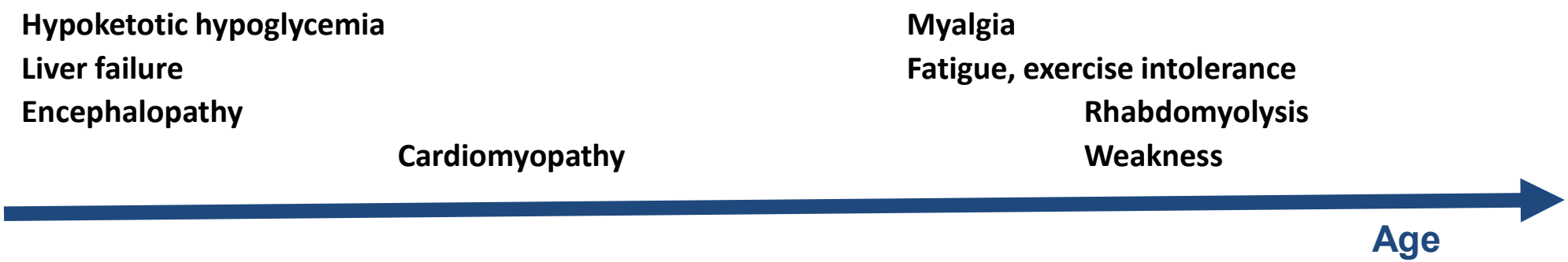
- *Maternal riboflavin level: 98 nmol/L (174-471)*
- *Maternal SLC52A1 (riboflavin transporter 1) variant*

Transient neonatal MADD due to maternal riboflavin deficiency…. How to manage next pregnancy?

Chiong, M et al. Transient multiple acyl-CoA dehydrogenation deficiency in a newborn female caused by maternal riboflavin deficiency. Molec. Genet. Metab. 92: 109-114, 2007.

Take home message

- *Range of MADD presentations from neonate to adult*



- Acylcarnitines: all elevated but C3 normal!

A 31 year old nurse with recurrent muscle pain

31 year old male

Works as a nurse, generally fit and well

- Played a round of golf
- Aching sensation in thighs and calves
- Completed the round of golf and drove himself home
- Sat down at home and then unable to get up again due to severe pain
- Took the next day off work, noticed that his urine was dark in colour
- Saw local doctor – CK 22,000 IU/L
- Pain settled over the course of a week

- Never hospitalised with this. No history of renal impairment

31 year old male

Referred to the mitochondrial team for investigation

Background history

- Normal motor development and very sporty as a child
- Played regular competitive football and rugby until his 20s

Recurrent episodes of exertional rhabdomyolysis:

- 17 years: Gardening – severe muscle pain, dark urine
- 26 years: Long walk in cold weather - severe muscle pain, dark urine

Physical examination

Normal

What would your approach to investigation be?

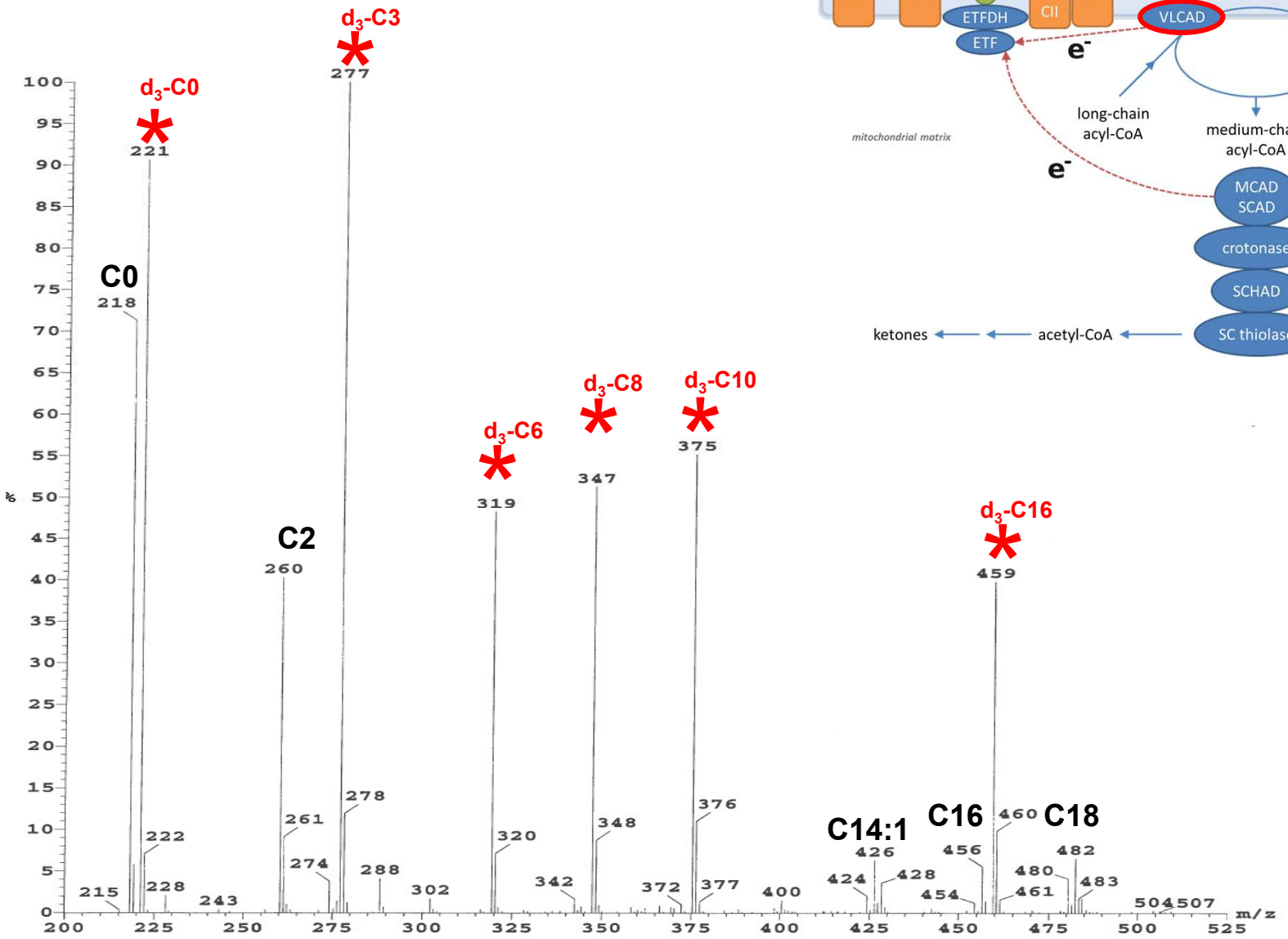
31 year old male - a few weeks later

Creatine kinase	498 IU/L (38-204 IU/L)
Muscle biopsy	Suggestion of increased mitochondrial staining. No frank ragged red fibres or SDH positive fibres and no evidence of cytochrome oxidase negative fibres. No lipidosis
Plasma acylcarnitine profile	Elevation of C14 - C18. Predominantly C14:1
Direct enzyme activity	Reduced muscle acyl-CoA dehydrogenase activity (C16 and C18 as substrates)

C16 or C18: citrate synthase ratio	Result	Normal reference
C16 (Palmitoyl-CoA)	0.02	0.071-0.184
C18 (Stearoyl-CoA)	0.008	0.031-0.159

Genetic analysis	Homozygous for p.Arg492Gln variant in the *ACADVL* gene

→ **Very long-chain acyl-CoA dehydrogenase deficiency**


d3-C0
d3-C3
d3-C6
d3-C8
d3-C10
d3-C16
C0
C2
C14:1
C16
C18
221
277
218
260
319
347
375
459
460
426
456
482
424
428
480
454
461
483
504507
222
261
278
320
348
376
215
228
243
274
288
302
342
372
377
400
%
m/z
CIV
C
CIII
Q
ETFDH
ETF
CII
CI
VLCAD
MTP
Mitochondrial Inner membrane
e-
e-
mitochondrial matrix
long-chain acyl-CoA
medium-chain acyl-CoA
acetyl-CoA
MCAD
SCAD
crotonase
SCHAD
SC thiolase
ketones
acetyl-CoA

31 year old male

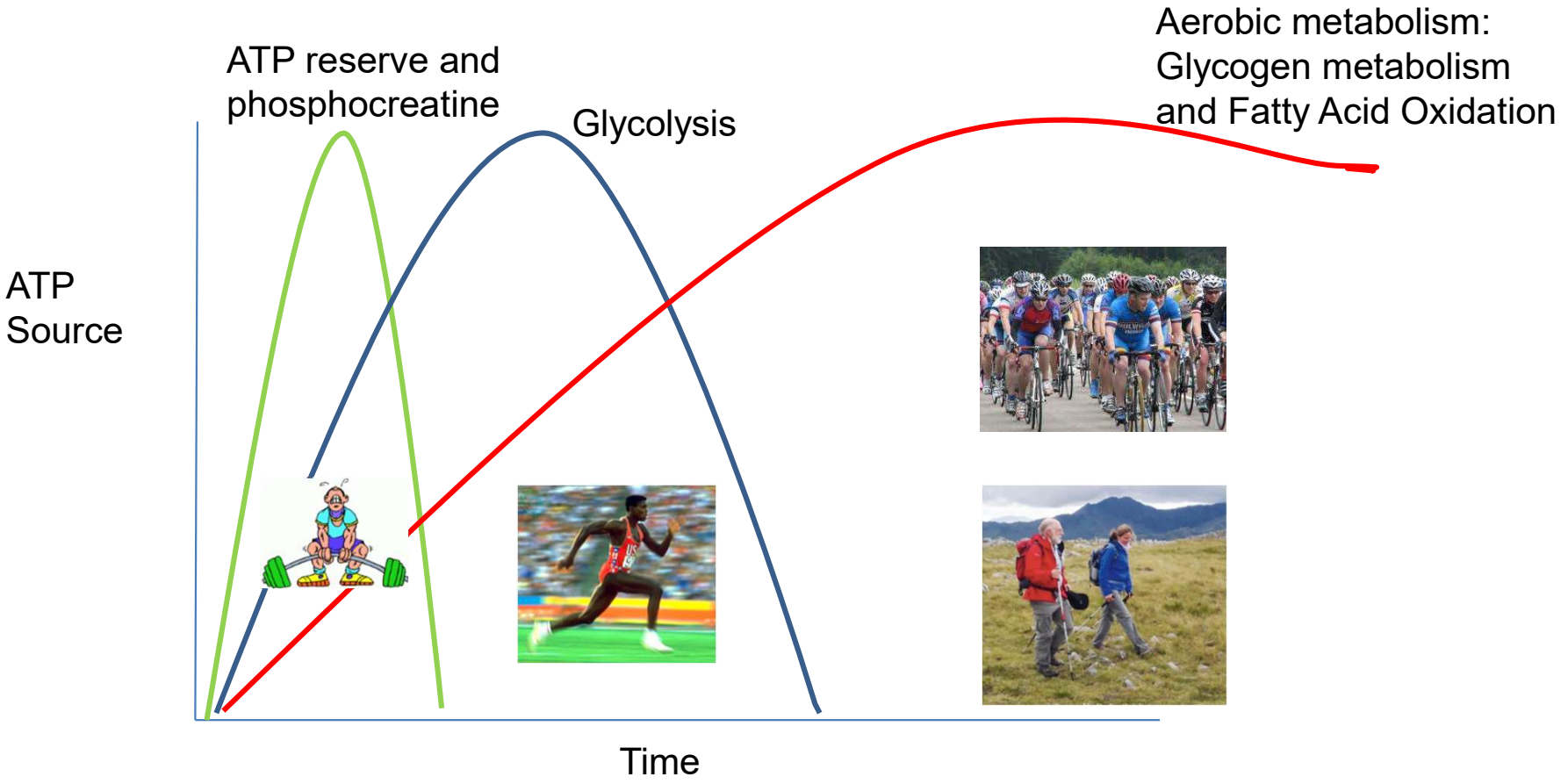
What else might you consider doing?

ECG and ECHO normal

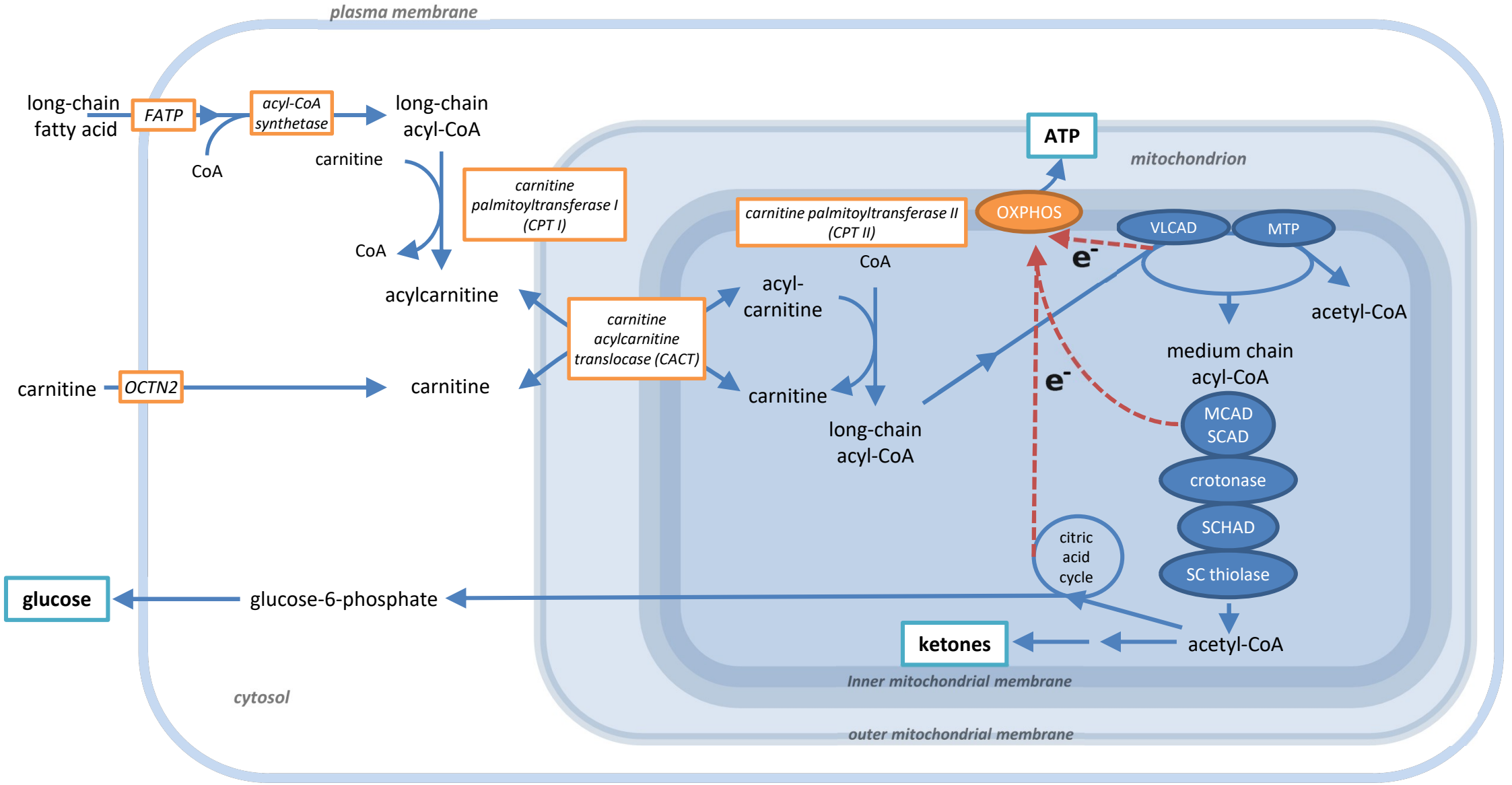
Family screening

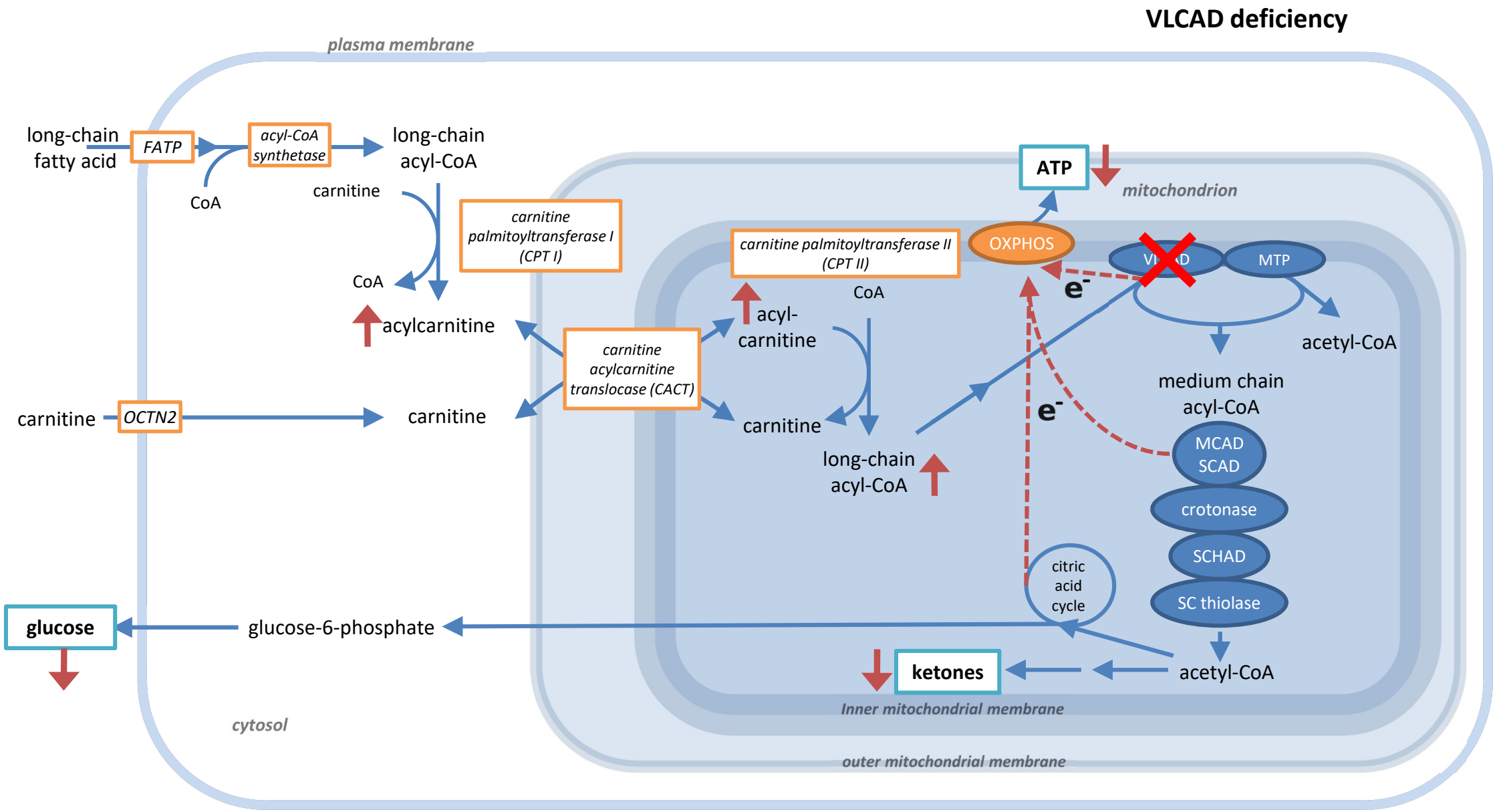
4 siblings – all reported well initially (but about 8 years later a younger brother presented with acute rhabdomyolysis)

Muscle energy metabolism

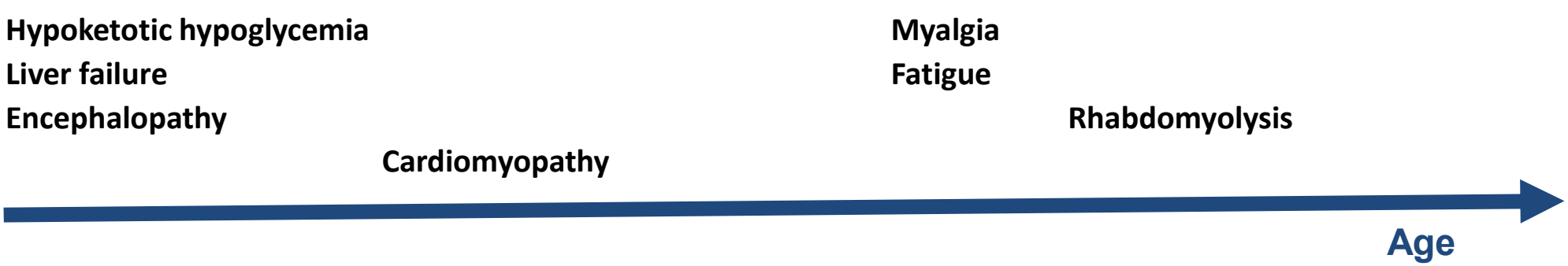


Mitochondrial fatty acid β-oxidation




VLCAD deficiency
plasma membrane
long-chain fatty acid
FATP
acyl-CoA synthetase
long-chain acyl-CoA
CoA
carnitine
carnitine palmitoyltransferase I (CPT I)
CoA
acylcarnitine
carnitine
OCTN2
carnitine
carnitine acylcarnitine translocase (CACT)
acyl-carnitine
carnitine
long-chain acyl-CoA
carnitine palmitoyltransferase II (CPT II)
CoA
ATP
mitochondrion
OXPHOS
e-
VLCAD
MTP
acetyl-CoA
medium chain acyl-CoA
e-
MCAD
SCAD
crotonase
SCHAD
SC thiolase
citric acid cycle
acetyl-CoA
glucose
glucose-6-phosphate
ketones
cytosol
Inner mitochondrial membrane
outer mitochondrial membrane

Long-chain Fatty Acid Oxidation Disorders (CPT2, VLCAD, TFP, LCHAD deficiencies)



31 year old male

What treatment would you advise him?

Avoid / limit precipitants – fasting, fever / infection, prolonged exercise, anaesthesia

Give an emergency regimen (fluids and glucose / dextrose)

Other options for more severe childhood onset cases

- *Provide regular calories (frequent daytime feeds, overnight pump feed)*
- *Restrict dietary (long chain) fat*
- *Supplement with medium chain triglyceride & fat-soluble vitamins*
- *Supplement with uncooked cornstarch*
- *Supplement with triheptanoin*

Take home messages

- In later-onset (‘milder’) cases - cardiac involvement is very rare
- A muscle biopsy is **not** a first line investigation for exercise-induced rhabdomyolysis… but an acylcarnitine profile is!
- Most of the diagnosis is in the history!