Fat Oxidation and Early Death - Recent Case Reports

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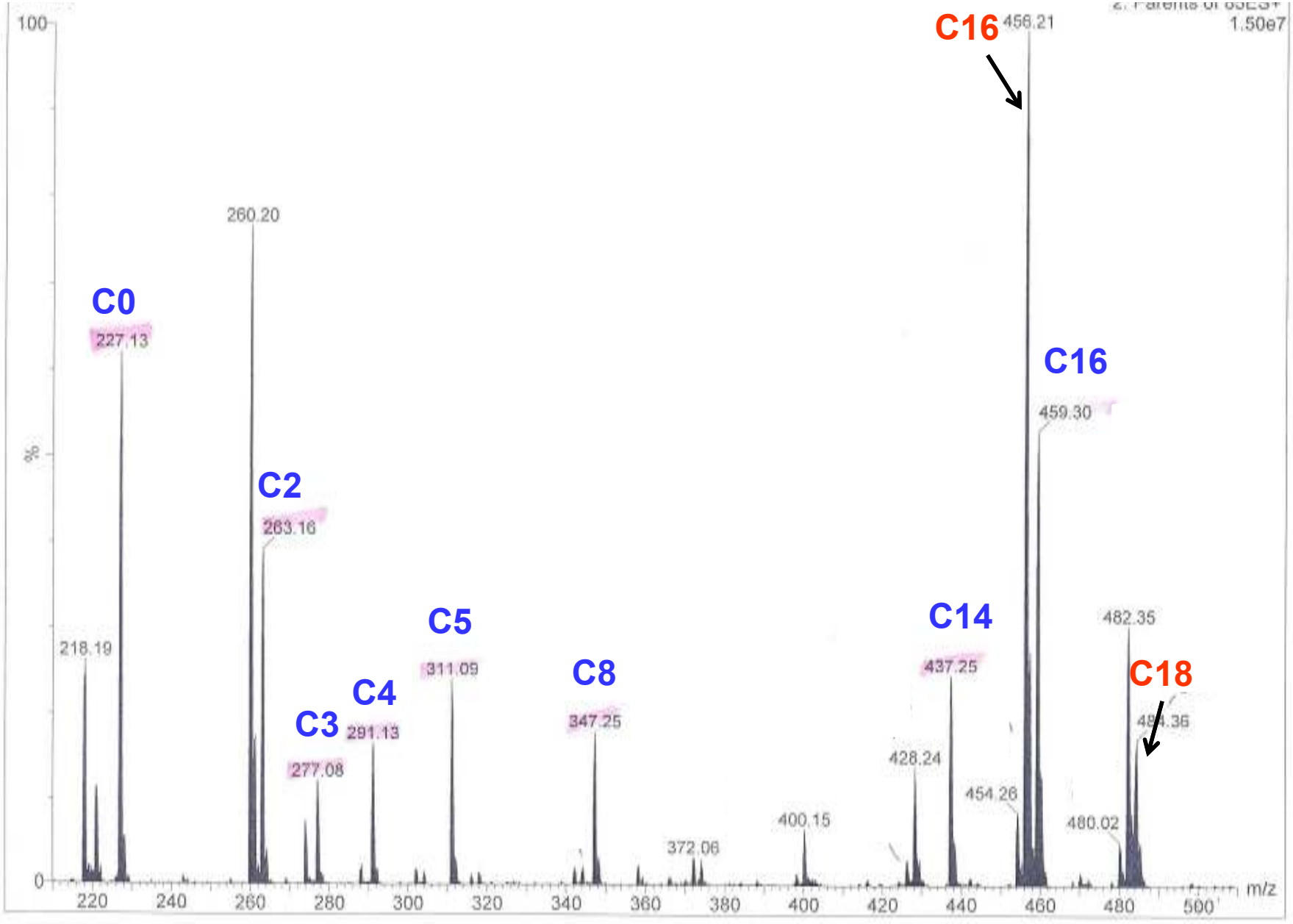
Case 1

- Male infant
- 2 days old
- Sudden collapse, resuscitation attempts unsuccessful and he died at home
- A&E
  - blood for cultures and bloodspots for acylcarnitine analysis collected
  - CSF collected (glucose and lactate)
  - other culture swabs
- Autopsy performed 3 days later
  – inc. blood spots taken for acylcarnitines


C16
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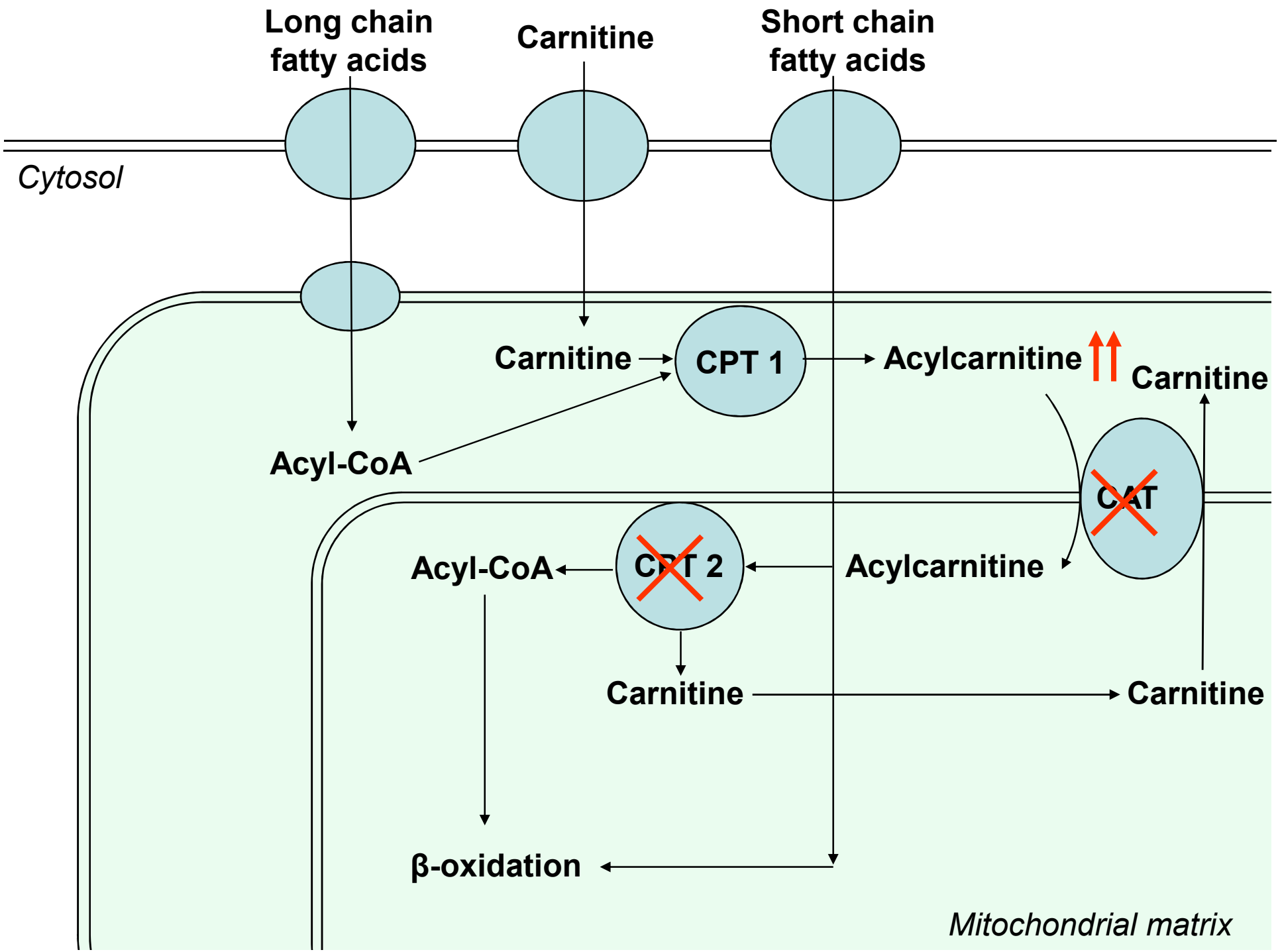
m/z

Acylcarnitine results (A&E sample)

Carnitine		Result (Admission) / umol/L	Reference Range
Palmitoleylcarnitine	(C16:1)	0.77	<0.40
Palmitoylcarnitine	(C16)	9.30	<4.00
Oleylcarnitine	(C18:1)	2.83	<2.30
Stearylcarnitine	(C18)	1.60	<0.80

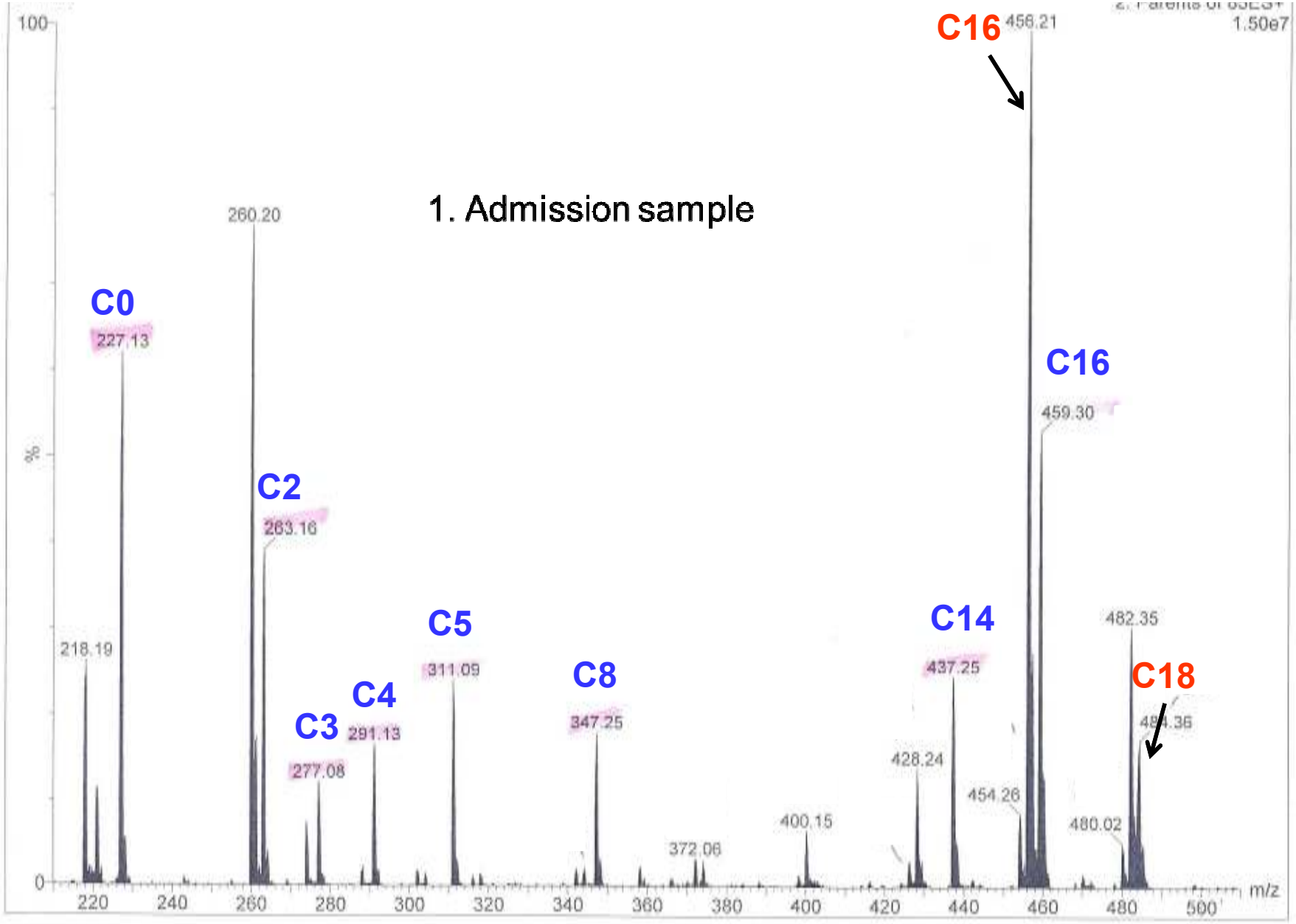
- Results consistent with defect in long chain fat oxidation (either CPT 2 or CAT deficiency).


Long chain fatty acids
Carnitine
Short chain fatty acids
Cytosol
Carnitine
CPT 1
Acylcarnitine
Carnitine
Acyl-CoA
CAT
Acyl-CoA
CPT 2
Acylcarnitine
Carnitine
Carnitine
β-oxidation
Mitochondrial matrix

Diagnosis

- Fibroblast studies required for enzyme analysis
  - excluded CPT 2 (the more common or the two)

- Mutation analysis for CAT
  - homozygous for p.Gly28Vys, c.82G>T pathogenic mutation


1. Admission sample
C16
456.21
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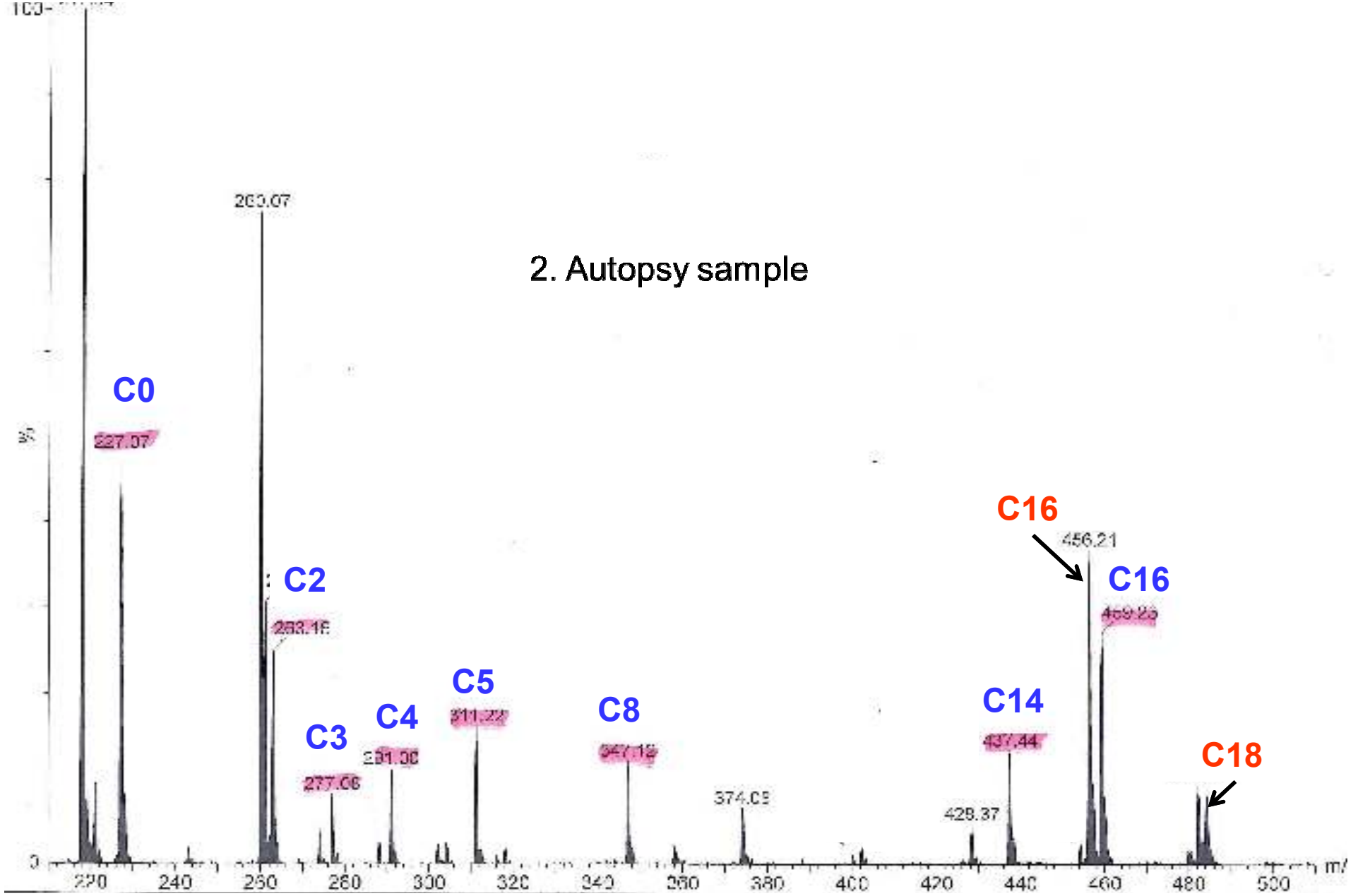
2. Autopsy sample



PM results

Carnitine		Result (Admission) / umol/L	Result (Autopsy) / umol/L	Reference Range
Palmitoleylcarnitine	(C16:1)	0.77	0.48	<0.40
Palmitoylcarnitine	(C16)	9.30	6.70	<4.00
Oleylcarnitine	(C18:1)	2.83	1.70	<2.30
Stearylcarnitine	(C18)	1.60	1.40	<0.80

- PM showed fat accumulation and abnormalities in liver, kidney and brain

Case 2

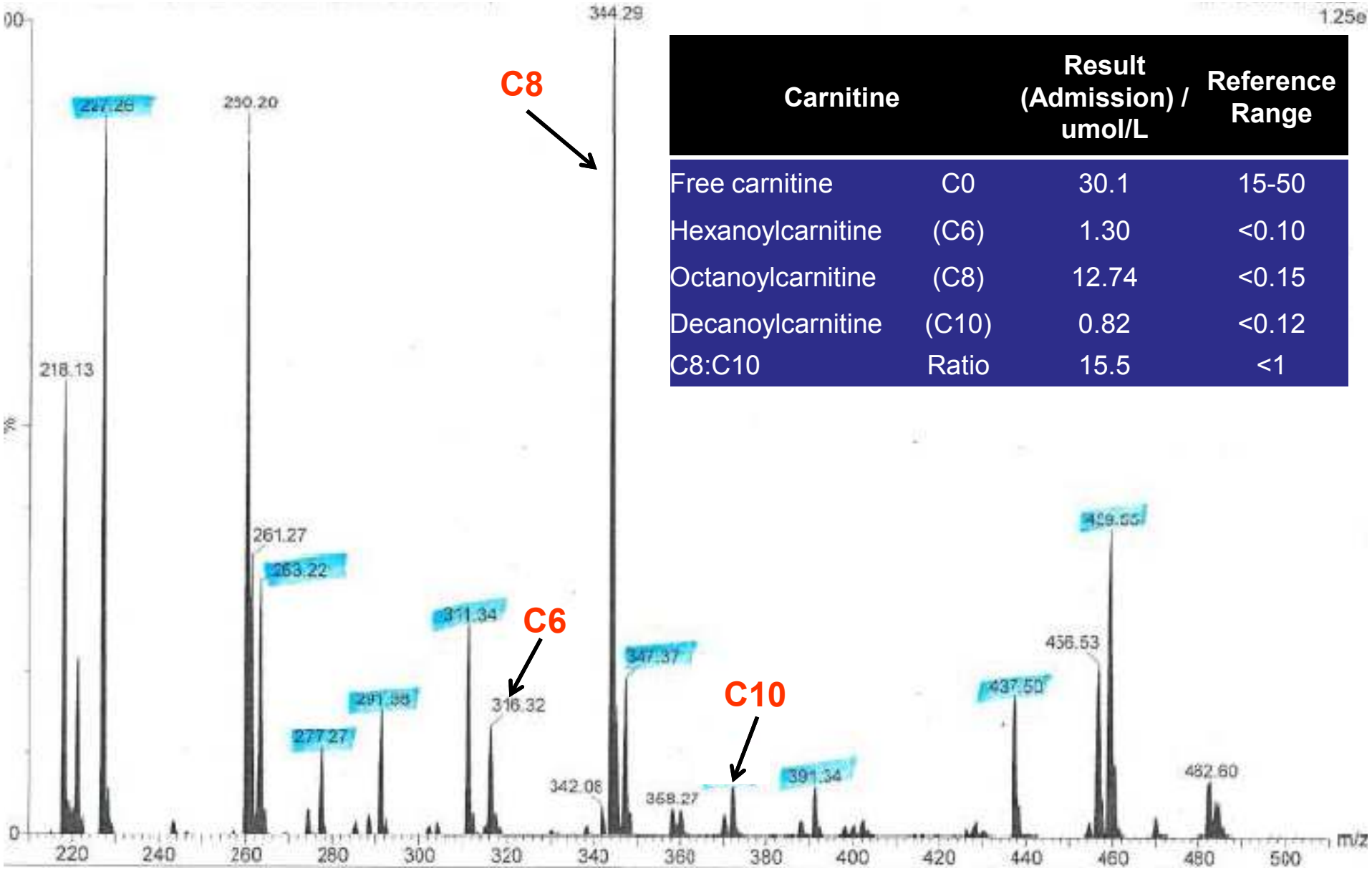
Case 2

- Term baby, parent's fist child
- OK for first 24 hours
- Day 2 – lethargy, hypoglycaemia, fitting - ?septicaemia (mum had infection prior to delivery) - fitting over next two days & mild cardiac arrythmias
- Day 4 cardiorespiratory arrest, 25 mins of resus - odd heart rhythm - severe brain damage Transferred to Leeds PICU
- Died on day 6
- Odd case – not thought to be enough evidence of sepsis (normal CRP)

Case 2

- Acylcarnitines requested on day 4 – clinical details: neonatal seizures.

- Urine metabolic screen requested day 6 – clinical details: HIE, abnormal cardiac, renal, liver functions - ?metabolic



Carnitine		Result (Admission) / umol/L	Reference Range
Free carnitine	C0	30.1	15-50
Hexanoylcarnitine	(C6)	1.30	<0.10
Octanoylcarnitine	(C8)	12.74	<0.15
Decanoylcarnitine	(C10)	0.82	<0.12
C8:C10	Ratio	15.5	<1

Case 2

- Organic acids:
  Increased dicarboxylic acids and suberyl glycine
  No hexanoyl glycine
  Increased lactate

- Mutation analysis
  1 x copy of common mutation found
  No other mutations currently identified

- Fat oxidation flux studies:
  Abnormal and consistent with MCADD
  (tritium release of labelled octanoate – 12% of controls)

NHS
National Patient Safety Agency

Rapid Response Report

NPSA/2011/RRR002

From reporting to learning

26 October 2011

Keeping newborn babies with a family history of MCADD safe in the first hours and days of life

Issue

Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is a rare inherited disorder where the body cannot metabolise fat properly. With a regular intake of food, individuals can live a normal healthy life, but prolonged fasting or illnesses with vomiting can lead to encephalopathy, coma or sudden death. The disease affects about one in 10,000 babies born in the UK but if both parents are MCADD carriers, there is a one-in-four chance of their child being born with MCADD. In the first 2-3 days of life, when regular feeding is not fully established, new born babies are heavily dependent on fat metabolism for their energy needs and those with MCADD are especially vulnerable to early neonatal death.

Screening for MCADD is part of the UK new born screening programme, which is offered to all babies in England at 5-8 days of age. A baby with a family history of MCADD should have special rapid testing 24 to 48 hours after birth on a blood spot card marked 'Family history of MCADD' (see resources from the UK Newborn Screening Programme Centre (UKNSPC)) but must also be given a special feeding regimen from the moment of birth (see resources from the British Inherited Metabolic Diseases Group (BIMDG)). Breastfeeding should be encouraged, but needs to be supplemented for babies born to families with a history of MCADD to minimise the risk of early neonatal death.

Evidence of harm

Between 1 January 2006 and 30 June 2011, the National Reporting and Learning System received two reports of deaths of newborn babies from MCADD who were born to families with a history of the disease. It appeared that although the mothers had mentioned the family history to healthcare staff when they were pregnant, the staff were not aware of the significance of MCADD, and therefore did not arrange any specialist referrals, special feeding regimen or observation. Six additional 'no harm' incidents reported to the NRLS indicated similar omissions, fortunately without adverse effects.

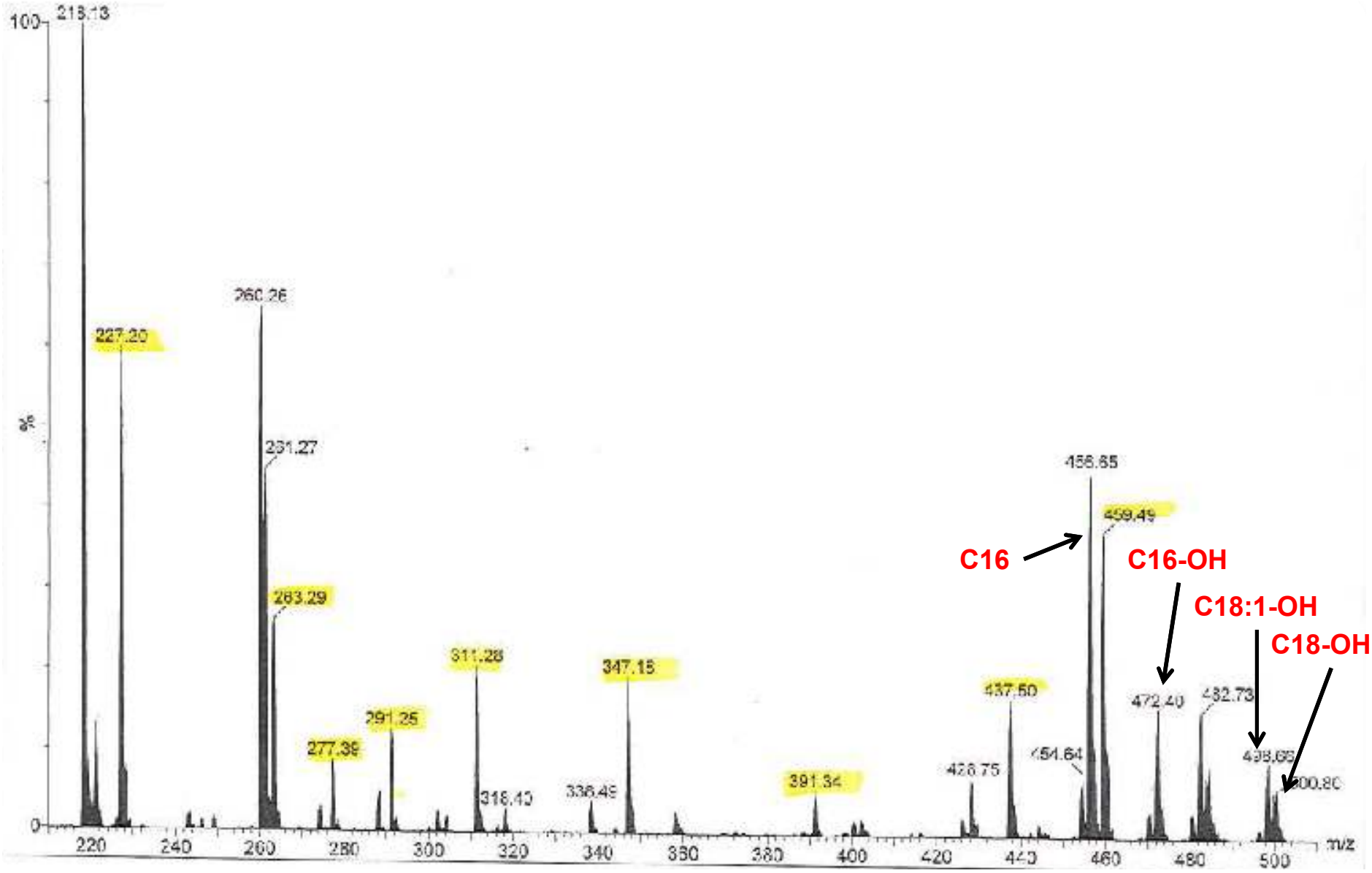
For IMMEDIATE ACTION by all General Practitioners, NHS organisations providing obstetric, midwifery, neonatal or paediatric services, and specialist centres for inherited metabolic disease.
The deadline for action complete is 26 April 2012.

Case 3

Case 3

- 2 day old baby
- Just arrived home
- Sudden collapse and death
- Baby noted to have not been feeding well

- As a result of SUDI box – bloodspots for acylcarnitines taken on admission to A&E shortly after death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C16
C16-OH
C18:1-OH
C18-OH
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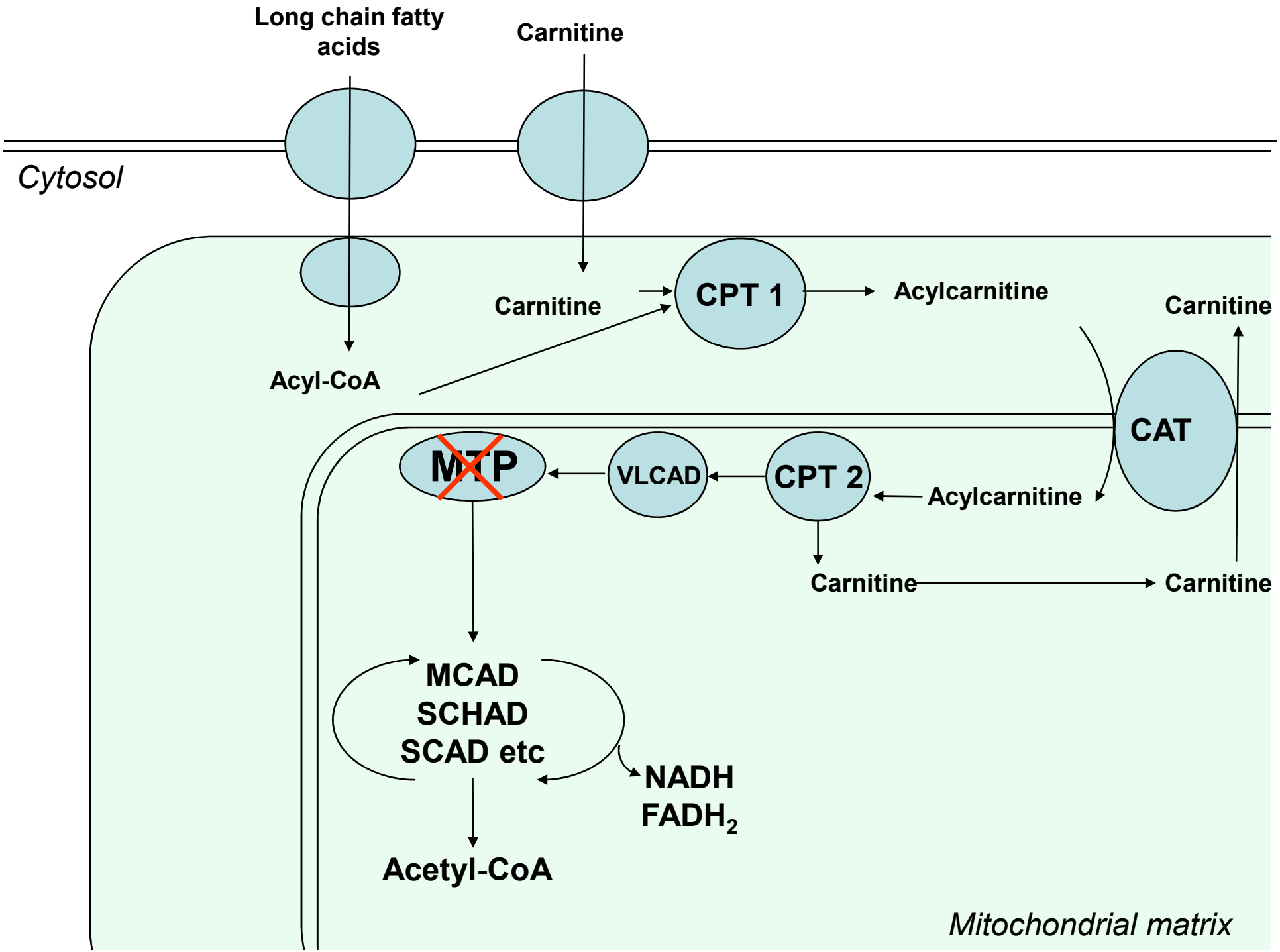
Quantitative results

Acylcarnitine	Notation	Result (umol/L)	Ref Range
Free carnitine	C0	81.4	15 – 50
Myristoylcarnitine	C14	1.03	<0.40
3-OH-myristoylcarnitine	C14-OH	0.26	<0.05
Palmitoleylycarnitine	C16:1	0.95	<0.40
Palmitoylcarnitine	C16	5.97	<4.00
3-OH-palmitoleylycarnitine	C16:1-OH	0.52	<0.20
3-OH-palmioylcarnitine	C16-OH	2.17	<0.10
Stearylcarnitine	C18	1.17	<0.80
3-OH-linoleylcarnitine	C18:2-OH	0.19	<0.05
3-OH-oleylcarnitine	C18:1-OH	1.23	<0.05

Diagnosis

- Profile consistent with a diagnosis of LCHADD (long chain hydroxyacyl-CoA dehydrogenase deficiency)
  either isolated or as part of Mitochondrial Trifunctional Protein Deficiency (MTP)

- MTP = a complex protein with three functions
  - LCHAD
  - thiolase
  - hydratase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CPT 1
Acylcarnitine
Carnitine
Acyl-CoA
CAT
MTP
VLCAD
CPT 2
Acylcarnitine
Carnitine
Carnitine
MCAD
SCHAD
SCAD etc
NADH
FADH2
Acetyl-CoA
Mitochondrial matrix

Case 3

- PM showed fatty infiltration of liver (microvesicular changes)

- Fibroblast studies:

  - abnormal fatty acid oxidation flux studies consistent with LCHADD/MTP deficiency

  - p.(Glu510Gln), c.1528G>C of *HADHA* gene (common mutation for LCHAD) – not detected

Case 3

- Enzyme analysis:
  LCHADD activity
  36 nmol/(min.mg protein) (ref 34-114)

  3-ketothiolase (long chain) (MTP)
  2 nmol/(min.mg protein) (ref 58-110)

  Low normal LCHADD activity and markedly reduced 3-ketoacyl-CoA thiolase activity. These results show the patient suffers from long-chain 3-ketoacyl-CoA thiolase/MTP deficiency.

- Mutation analysis:
  HADHB gene sequence and two mutations found c.1292T>C (p.Phe431Ser) and c.1301C>T (p.Thr434Ile)

Case 3 Con't

- By this stage mum was known to be pregnant again:
  - ?prenatal a possibility
  - time of the essence
  - analysis performed in Amsterdam

- Chorionic villus biopsy samples
  - LCHAD activity 79% of mean control (near normal)
  - 3-ketothiolase (long chain) (MTP) 33% of control (reduced activity)
  - No definite conclusion → further studies required

- Repeat CVB
  - Normal LCHAD activity
  - Slightly reduced 3-ketothiolase (long chain) (MTP)
  - Conclusion: foetus not affected with MTP deficiency

- Molecular analysis subsequently showed unborn baby to be a carrier

- Acylcarnitine analysis after birth – no abnormalities, baby well.

Case 4

Case 4

- Initial presentation
  - female, 10 months old
  - developmental delay, hypotonic, mild facial dysmorphic features

- Urine metabolic screen
  - organic acid analysis showed a small peak of suberyl glycine

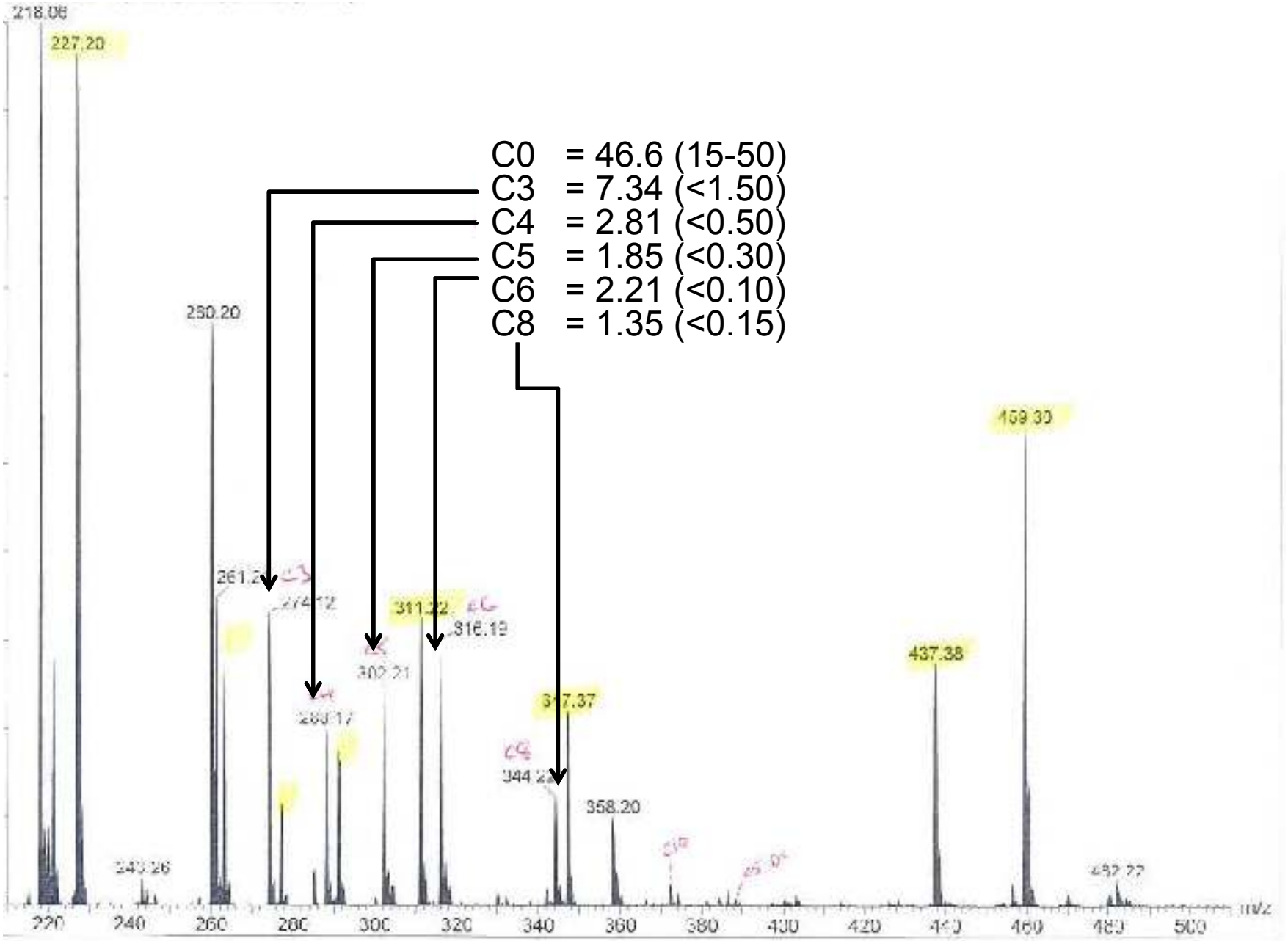
Case 4

- Organic acids
  - peak of suberyl glycine continued to be the only abnormality.
  Presence was intermittent
  peak in 2/4
  trace in 1/4
  not detected in 1/4 urine samples

- Acylcarnitines
  - no abnormality detected

Case 4

- Aged 15 months
- Acute admission
  - respiratory distress
  - arrested and died
- Acylcarnitines from sample taken in A&E….


C0 = 46.6 (15-50)
C3 = 7.34 (<1.50)
C4 = 2.81 (<0.50)
C5 = 1.85 (<0.30)
C6 = 2.21 (<0.10)
C8 = 1.35 (<0.15)
218.08
227.20
250.20
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311.22
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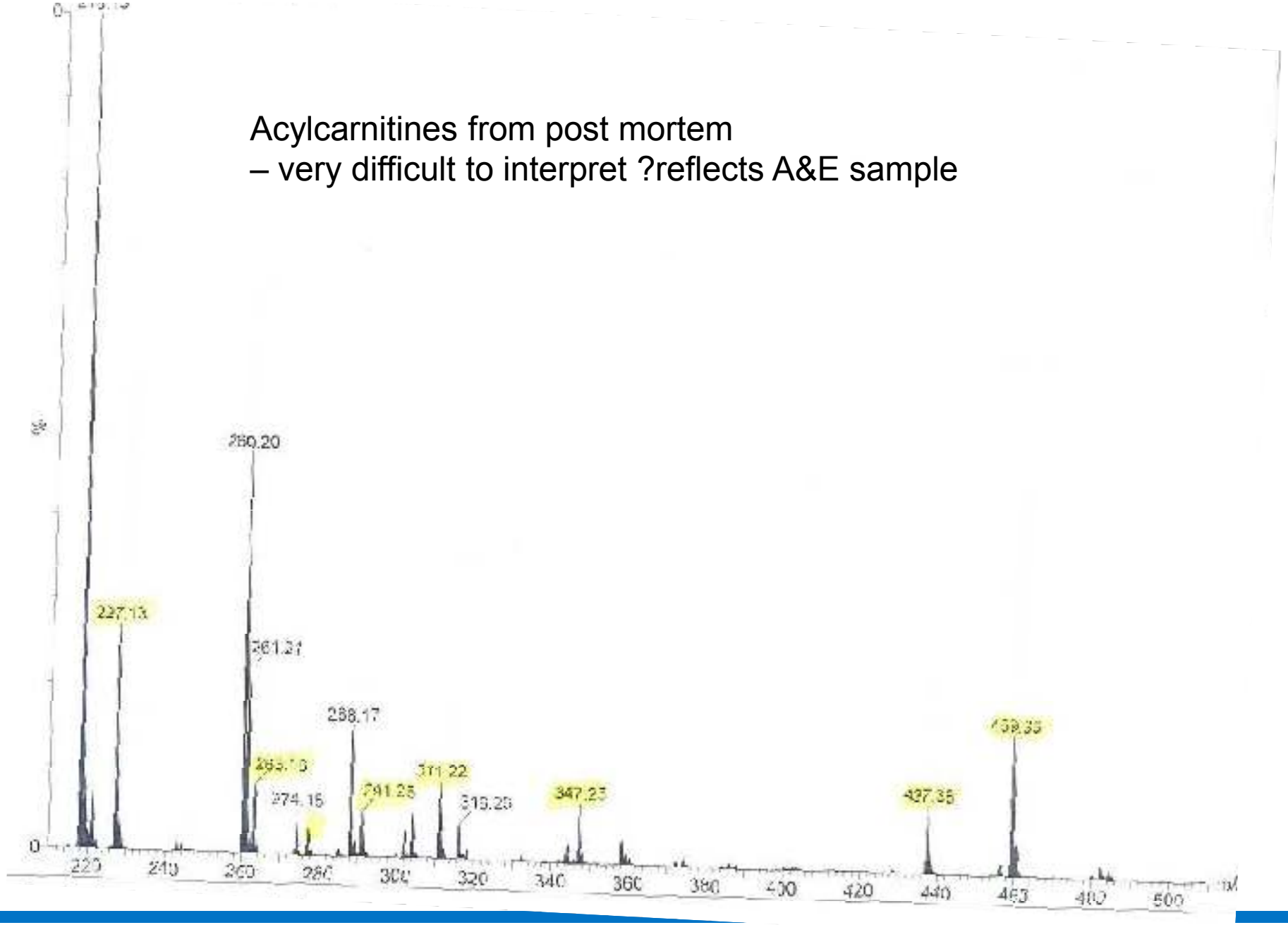
Acylcarnitines from post mortem
– very difficult to interpret ?reflects A&E sample



?metabolic cause

- Fat oxidation studies: normal
  - excludes almost all disorders of fat oxidation

  - ?MADD variant (multiple acyl-CoA dehydrogenase deficiency)

  - ?riboflavin transporter defect (no mutations found)

Summary/Discussion points

- Inherited disorders of fatty acid oxidation are a rare but significant cause of SUDI (?underreported)

- Diagnosis is important
  - future pregnancies: prenatal diagnosis often possible
  - early management/testing of future siblings critical (e.g. MCADD)

- Acylcarnitines (bloodspots, bile, ?urine, ?CSF)
  - initial test for investigating these disorders

  - taken **as close to time of death as possible** aids interpretation
  (not always easy or thought of immediately after death)

  - further studies often req fibrobalsts and/or mutation analysis