A Case of Metabolic Acidosis

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History

- A healthy girl born at term of an uncomplicated pregnancy
- Apgar score 9
- Consanguineous parents of Pakistani origin
- Readmitted at 5 days
- Floppy, drowsy, poor feeding, hyporeflexic

On Ward Testing –Day 5

- Blood glucose 5.5mmol/L
- Blood gases:
  - pH 7.1 (7.35-7.45)
  - *P*aO_2 10.2 (9.3-13.3 kPa)
  - *P*aCO_2 3.1 (3.6-5.3 kPa)
  - HCO_3 16.4 (21-28mmol/L)
  - Anion gap 22 (8-16mmol/L)

- Mixed metabolic acidosis
- Urine dipstick ketones +

Basic Biochemistry / Haematology – Day 5

- U&Es
  - Na 148mmol/L
  - K 4.0 mmol/L
  - Creatinine 58 μmol/L
  - Urea 15.1mmol/L
  - Adjusted calcium 1.8 mmol/L

- FBC
  - Low WCC (Neutropaenia)
  - Low Platelets (Thrombocytopaenia)

- Ammonia requested urgently 821μmol/L (Normal<150μmol/L)
- Lactate 4.1 (Normal 0.7-3.4 mmol/L)

Differential Diagnosis

- Organic Acidurias
  - Methylmalonic aciduria
  - Propionic aciduria
  - Isovaleric aciduria
- Disorder of biotin metabolism
- Respiratory chain disorder (but would not expect hyperammonaemia)
- Fatty acid oxidation defect (but would usually expect hypoglycaemia and no hyperammonaemia)

Urine organic acids are the key to diagnosis!

Further Tests Required

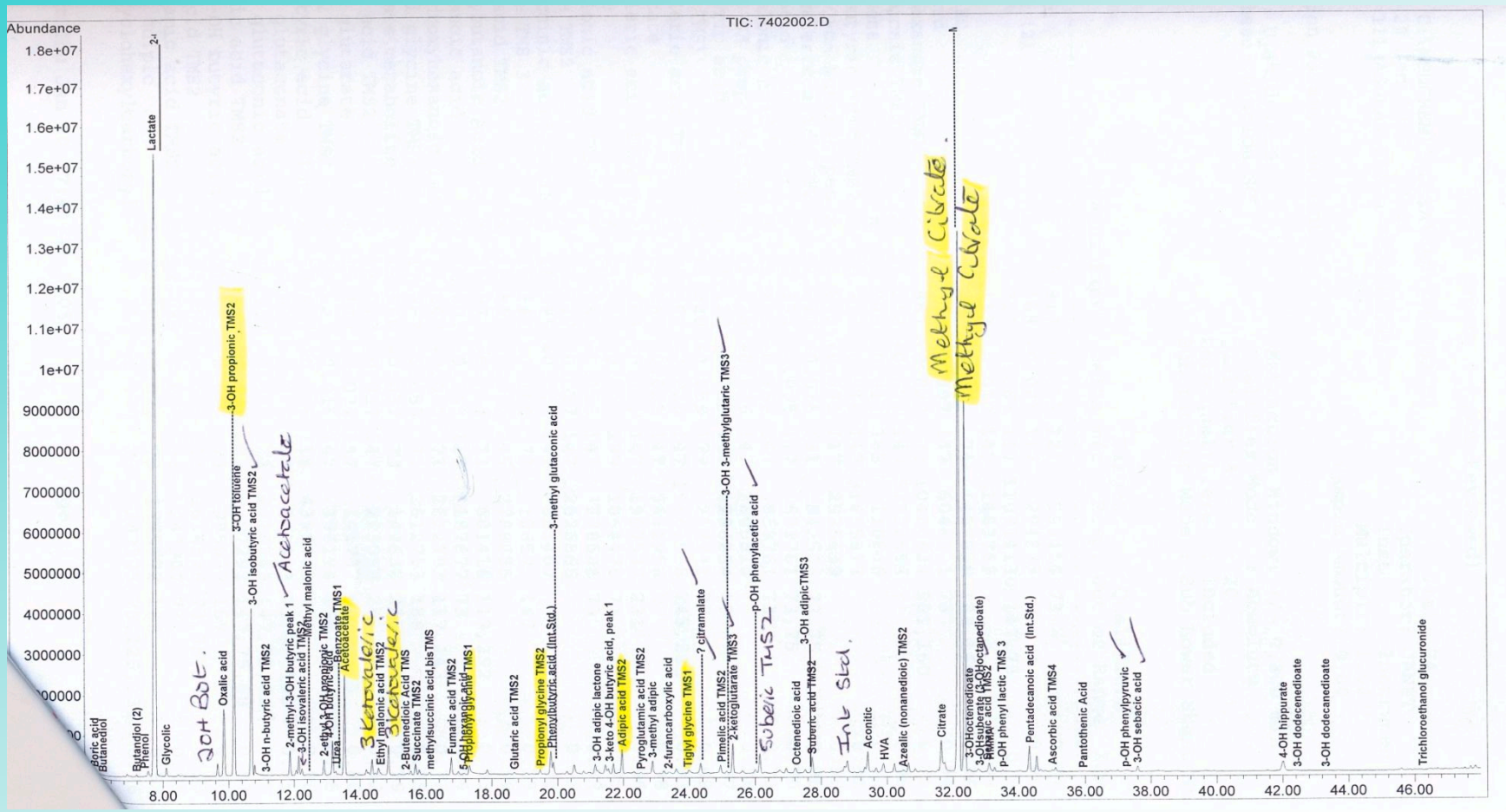
- Plasma amino acids
- Carnitine status
- Acylcarnitines
- Urinary organic acids

Acylcarnitines & Amino Acids – Day 6

- Acylcarnitines
  - Free carnitine 10 (Normal 15-50)
  - Propionylcarnitine (C3) 20 (Normal <2.5)
  - All other acylcarnitines low
- Plasma and urine amino acids
  - Non-specific increase in all amino acids (often due to dehydration)
  - Elevated glycine

Urine Organic Acids Trace – Day 7

Increased excretion of 3-hydroxypropionate, propionyl glycine, tiglylglycine and methylcitrate

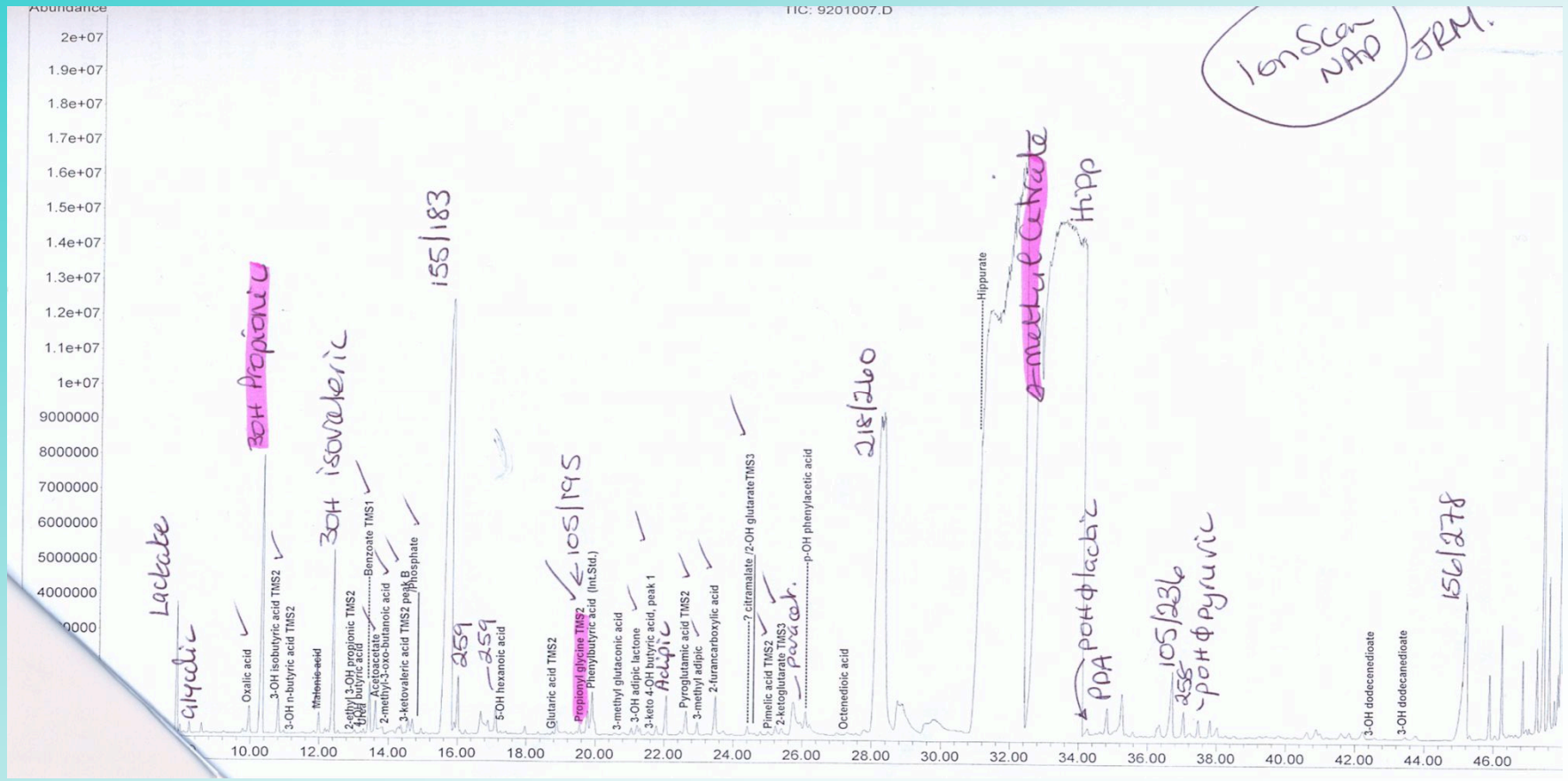


Diagnosis

- Propionic Aciduria
- Treatment started (see later slide on treatment options)

Urine Organic Acid Trace – Day 8
24 hrs of Treatment

3OH propionic, propionyl glycine, methylcitrate, hippurate



Organic Acidurias

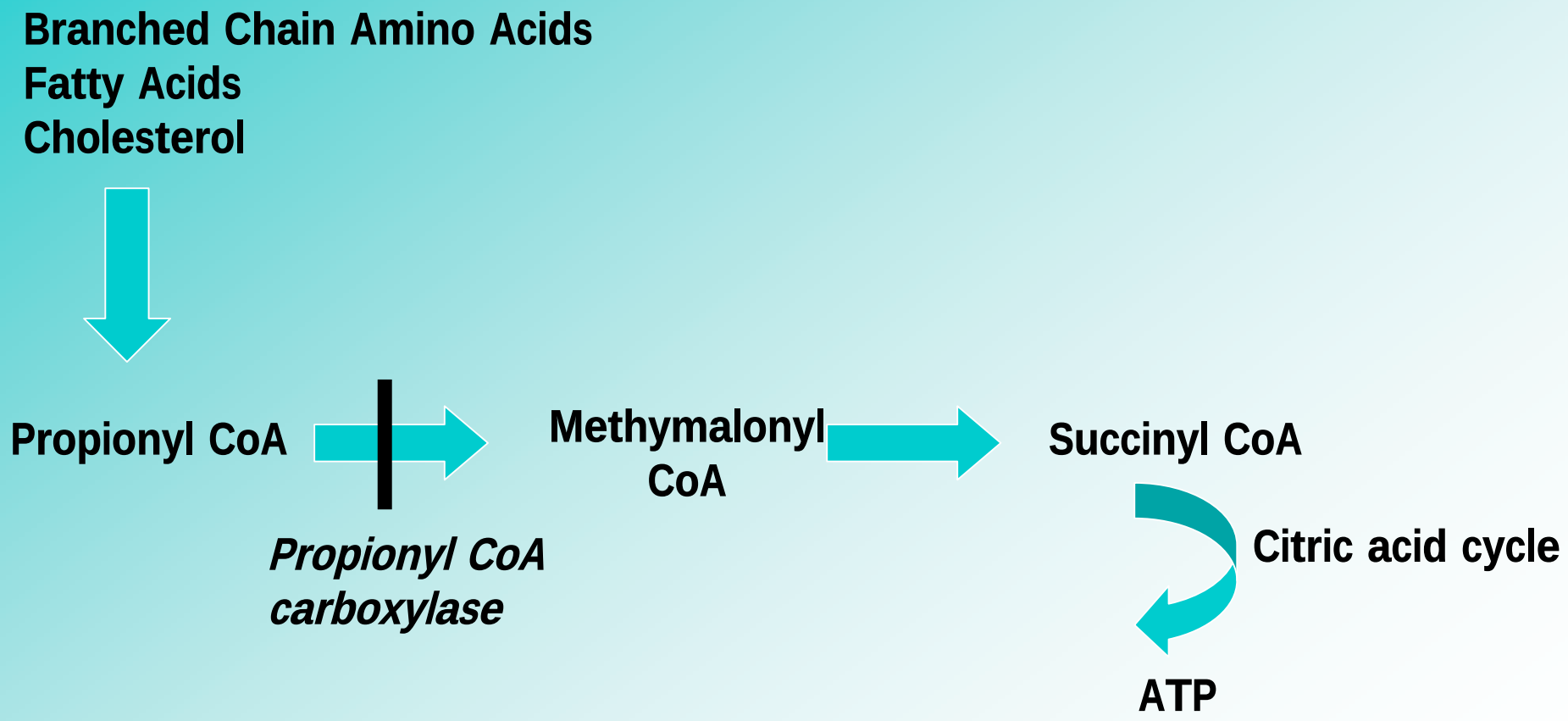
- These are disorders of intermediary metabolism
- There is a characteristic accumulation of carboxylic acids identified by GC/MS analysis of urine
- Many are due to disorders of branched chain amino acid metabolism
- There is Intramitochondrial accumulation of organic acid CoA intermediates.
- For further information see the Organic Acid Disorders module on:-

http://www.metbio.net/metbioTrainingDocuments.asp?s=1

Propionic Aciduria

- Autosomal recessive
- Frequency ~ 1 : 100,000 live births
- PropionylCoA carboxylase deficiency
- Inability to catabolise 4 essential amino acids
  - Isoleucine, valine, threonine and methionine
- PropionylCoA inhibits enzymes in the citric acid and urea cycles leading to lactic acidaemia and hyperammonaemia

Metabolism of Propionic Acid



Clinical features

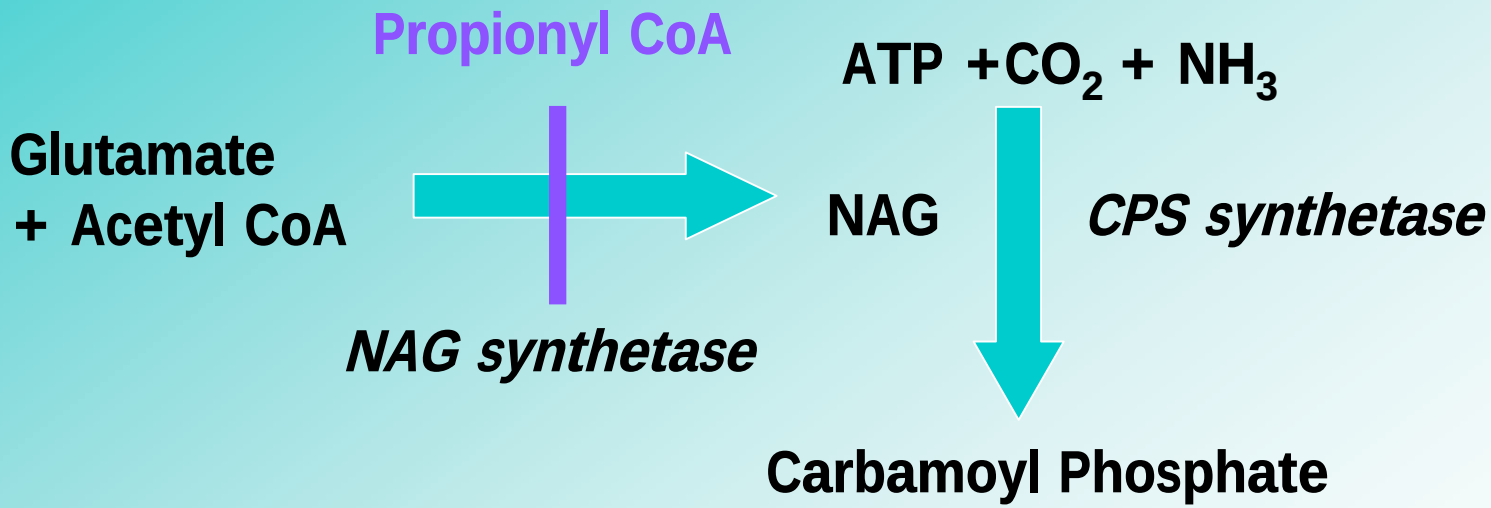
- Onset towards the first week of life
  - Encephalopathy
  - Lethargy
  - Feeding problems
  - Dehydration
  - Hypotonia
  - Tachypnoea

Laboratory Results

- Ketosis
- Raised lactate
- Raised ammonia
- Variable glycaemia
- Low calcium
- Neutropaenia
- Thrombocytopaenia

Hyperammonaemia in Organic Acidurias

This is believed to be due to inhibition of N-acetylglutamate synthetase by propionylCoA. N-acetylglutamate is an important activator for carbamoyl phosphate synthetase-the first step of the urea cycle.



NAG : N-Acetylglutamate
CPS: Carbamoyl phosphate

Diagnostic tests

- Amino acids (urine /plasma)
  - High glycine
- Acylcarnitines
  - Low carnitine
  - Increased propionylcarnitine (C3)
- Urine organic acids
  - High 3-hydroxypropionate and methylcitrate
  - High ketones

Treatment - Acute

- Sodium benzoate
- Carnitine
  - Binds acyl groups of toxic organic acid metabolites and makes them increasingly water soluble so they are readily excreted in urine
  - If carnitine is depleted fatty acid oxidation can be compromised, hence it needs to be replaced to restore energy production.
- Glucose and insulin to stop catabolism and promote anabolism
- Metronidazole to remove ammonia-producing bacteria.

Treatment – Long Term

- Low protein diet (restricted intake of branched chain amino acids)
- L-carnitine supplementation ~100mg/day
- Liver transplantation

- Monitoring
  - Growth, weight
  - Ammonia
  - Plasma amino acids (nutrition)

Complications

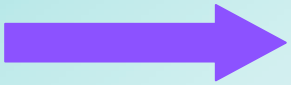
- Mental retardation
- Movement disorders
- Osteoporosis
- Pancreatitis
- Cardiomyopathy

Prenatal diagnosis

1)Assay of propionyl CoA carboxylase

- **Chorionic villus biopsy (CVB) at ~ 9-12 weeks**
- **Cultured amniotic fluid cells (16-18 weeks)**

propionyl-CoA carboxylase



propionic acid + *sodium bicarbonate → **methylmalonic acid + *CO_2**

2)Measurement of metabolites in amniotic fluid supernatant (>13 weeks)

Summary

- Consider an inborn error of metabolism when there is clear evidence of a metabolic crisis and no obvious cause (such as overwhelming sepsis)
- Measure ammonia (urgently!)
- It is important to reach an accurate diagnosis as this affects treatment and survival
- Achieving a diagnosis is critical even if the child does not survive because it gives:-
  - closure for the family and professionals
  - the possibility of prenatal diagnosis