A Case of Metabolic Acidosis

Sarah Glover

St James University Hospital, Leeds

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)
 - PaO₂ 10.2 (9.3-13.3 kPa)
 - $-PaCO_2$ 3.1 (3.6-5.3 kPa)
 - HCO₃ 16.4 (21-28mmol/L)
 - Anion gap 22 (8-16mmol/L)
- Mixed metabolic acidosis
- Urine dipstick ketones +

Basic Biochemistry / Haematology – Day 5

- Na
- K
- Creatinine
- Urea
- Adjusted calcium

148mmol/L 4.0 mmol/L 58 μmol/L 15.1mmol/L 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

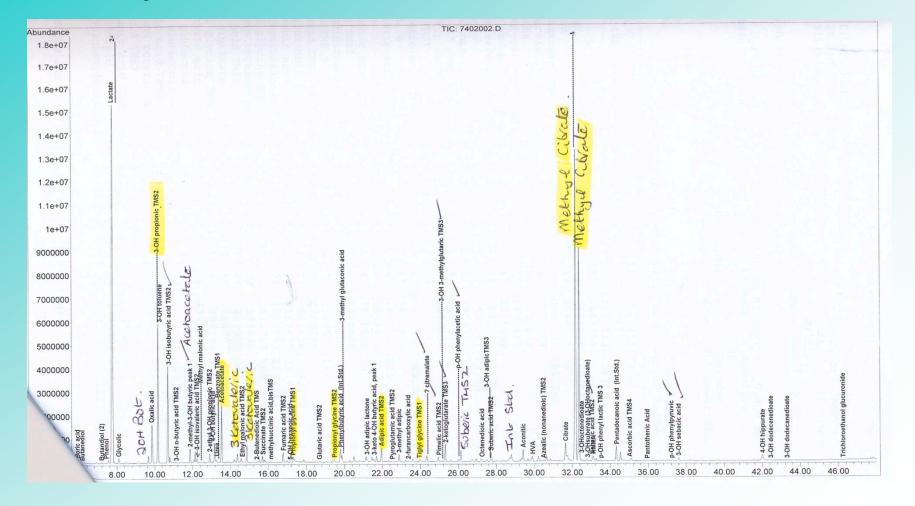
Acylcarnitines & Amino Acids – Day 6

Acylcarnitines

- Free carnitine 10 (Normal 15-50)
- Propionylcarnitine (C3) 20 (Normal <2.5)</p>
- 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

Abundance			TIC: 9201007.D		
2e+07					SON KROW
1.9e+07				(100 SLOPP SPM.
1.8e+07					
1.7e+07				10	
1.6e+07				. 7 8	
1.5e+07	S	0		. Hipo	
1.4e+07	c	ē		M / M	
1.3e+07		Ő		Hippurate	
1.2e+07	Joh Appioni				
1.1e+07	- J		0	Man	
1e+07	BOURLEVIC		0 ore/site	4	
9000000	yes of		N OC		
8000000	SO /	N I	C acid		
7000000	7	50	acetic		\sim
6000000	2 V 30H Benzoate TMS1	269 Invance acid Invance acid Invance acid Program 1952 Program (IntStu) In 100 Acid (IntStu) In 100 Acid (IntStu) In 100 Acid (IntStu) Internetion Acid (IntStu) Internetion Acid (IntStu) Acid (IntS	OH phenylacetic acid	20	848/95
5000000	CLCC Introduce T	state in the second sec	HO-d-	ict ict	5
4000000	Lacka eid TMS2 v	ints:	1:	36	121
0000	L(ms2 p	159 182 182 182 182 182 182 182 182 182 182	3	HC C	5
	Cilyculi Lackad	S-OH hexanoic acid S-OH hexanoic acid giutaric acid TMS2 Propiony giptene TMS2 Propiony giptene TMS2 Propiony giptene tMS2 - Propiony giptene acid Acid Politic acid, peal Acid Propionic acid acid Acid Propionic acid acid acid Acid Propionic acid Acid Propionic acid acid Acid Propionic acid acid Acid Propionic acid acid Acid Propionic Acid Propionic Acid Acid Acid Propionic Acid Acid Acid Propionic Acid Acid Acid Propionic Acid	MS2 V Dovc	PDA POH & lach's	dioate
	CITYCLI CITYCLI Oralic acid 3-OH Isobury OH n-buryric acid Matonia eadd Matonia eadd Matonia eadd CITYCL 2000	adipic to the same of the same	acid T glutara	0	lecene
	Cilyculi Lack Cilyculi Consile acid Oxalie acid Miss John Subuynie acid Miss Manuso acid Miss Manuso acid Miss Manuso acid Miss Carefordiano acid Miss Aktovalence acid Miss pagk	5:0H hexanoic acid 5:0H hexanoic acid Gluraric acid TMS2 Gluraric acid TMS2 Phenybluyrics a 2.methyl glutaconic acid 3.keto 4.0H adpic lecton 3.keto 4.0H uhyric acid 3.methyl ddpic 3.methyl ddpic	Pimelic acid TMS2 24keoglutanate TMS3 Povid OL Octemedioic acid	4	3-OH dodecenedioate
	10.00 12.00 14.00	16.00 18.00 20.00 22.00 24.00	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	32.00 34.00 36.00 38	3.00 40.00 42.00 44.00 46.00

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:-

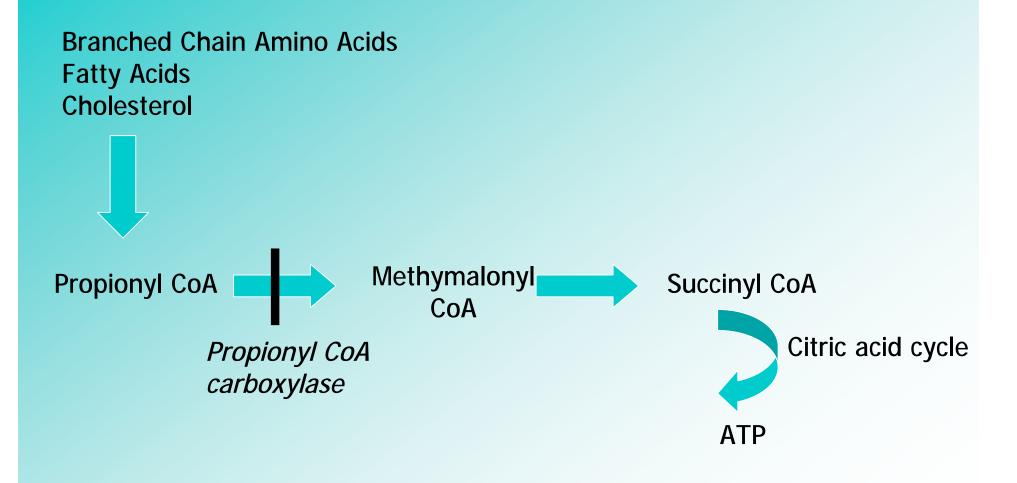
http://www.metbio.net/metbioTrainingDocuments.asp



Propionic Aciduria

- Autosomal recessive
- Frequency ~ 1 : 100,000 live births
- PropionyICoA 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

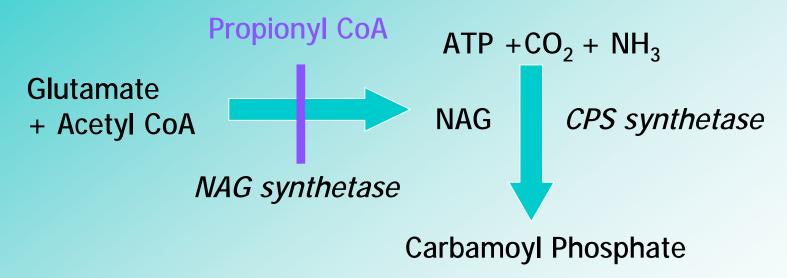
- Onset towards the first week of life
 - Encephalopathy
 - Lethargy
 - Feeding problems
 - Dehydration
 - Hypotonia
 - Tachypnoea

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)

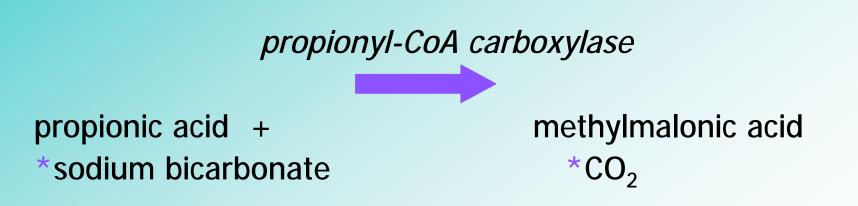
Complications

- 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)



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