Carbohydrate training day

Galactose, fructose etc

Mary Anne Preece
Consultant Biochemist
Birmingham Children’s Hospital
Galactose

- lactose (glucose-galactose)
- primary CHO source in milk
- provides 40% of energy in neonates
- symptoms appear early in life

Metabolism
- formation of glucose-1-phosphate ie acts as energy source especially in infants
- formation of galactosides via UDPgal
- minor pathways
  - formation of galactitol
  - formation of galacturonic acid
Inborn errors of galactose metabolism

- galactose-1-phosphate uridylyl transferase deficiency (classical galactosaemia)
- galactokinase deficiency
- epimerase deficiency
- all autosomal recessive
Galactose metabolism

galactose → galactose-1-P

UDPglucose → glucose-1-P

UDPgalactose → glycolipids
Galactose-1-phosphate uridyl transferase
Classical galactosaemia

- normal birth weight
- failure to regain birth weight
- symptoms in second half of 1st week
  - refusal to feed
  - vomiting
  - jaundice
  - lethargy
  - hepatomegaly
  - oedema
  - ascites
  - death due to liver/kidney failure, sepsis (E coli)
- cataracts within days or weeks
Classical galactosaemia

- Biochemical abnormalities
  - Hypoglycaemia
  - Conjugated hyperbilirubinaemia (initially unconj)
  - Abnormal liver enzymes
  - Coagulopathy
  - Hypophosphataemia
  - Reducing substances
  - Aminoaciduria
  - Hyperphenylalaninaemia
BPSU 3 year study (1998-1990) conclusions

- **incidence (UK)**: 1 in 44000

- **diagnosis**
  - clinical features/ biochemical: 25
  - clinical features: 12
  - family history: 6
  - biochemical tests: 3

- **commencement of treatment**
  - 90% by 1 month
  - 75% by 3 weeks
  - 67% by 2 weeks
Classical galactosaemia - incidence

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>UK</td>
<td>1 in 44,000</td>
</tr>
<tr>
<td>Eire</td>
<td>1 in 26,000</td>
</tr>
<tr>
<td>Australia</td>
<td>1 in 33,000</td>
</tr>
<tr>
<td>USA</td>
<td>1 in 62,000</td>
</tr>
<tr>
<td>Japan</td>
<td>1 in 667,000</td>
</tr>
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</table>
Diagnosis of classical galactosaemia – the practicalities

- urine sugars
- erythrocyte galactosaemia screen (Beutler)
- quantitative galactose-1-phosphate uridyl transferase (erythrocyte/fibroblast)
- erythrocyte galactose-1-phosphate
- mutation analysis
- urine galactitol
Urine sugars

® Clinistix
  § specific for glucose

® Benedict’s
  § reacts with reducing substances including reducing sugars
  § glucose, galactose, fructose, lactose – POSITIVE
  § sucrose – NEGATIVE
<table>
<thead>
<tr>
<th>Clinitix</th>
<th>Benedict's</th>
<th>Sugars present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Glucose only</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Non glucose reducing substance(s)</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Glucose +/- other non glucose reducing substance(s)</td>
</tr>
</tbody>
</table>
Urine sugars - pitfalls

- rely on dietary intake
- Clinistix and Clinitest are confused
- can have positive Clinistix in galactosaemia
- galactosuria may be secondary to liver failure
Sugar chromatography

Ribose Marker
Glucose
Galactose
Lactose

2.5 mmol standard
10 mmol standard
RA.
RA.
Beutler test

UDPgluc*  gal-1-P*  NADP*
Beutler test

UDPgluc*          gal-1-P*

GALT

NADP*

Rbc enz including G6PD
Beutler test

UDPgluc* \rightarrow \text{GALT} \rightarrow \text{gal-1-P*}

UDPgal \rightarrow \text{gluc-1-P}

\text{NADP*} \rightarrow \text{Rbc enz including G6PD} \rightarrow \text{ribose-5-P}

\text{NADPH}
Beutler test in galactosaemia

**UDPgluc**

**gal-1-P**

**UDPgal**

**gluc-1-P**

**NADP**

**ribose-5-P**

**NADPH**

**Rbc enz including G6PD**

[Diagram showing the metabolic pathway involving UDPgluc, gal-1-P, UDPgal, gluc-1-P, NADP, ribose-5-P, and NADPH, with a red X indicating a block in the G6PD enzymatic activity.]
## Beutler Test

<table>
<thead>
<tr>
<th>Test Type</th>
<th>1 Hour</th>
<th>2 Hour</th>
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</thead>
<tbody>
<tr>
<td>Baby B.</td>
<td><img src="image1" alt="Results" /></td>
<td><img src="image2" alt="Results" /></td>
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<tr>
<td>Homozygote</td>
<td><img src="image3" alt="Results" /></td>
<td><img src="image4" alt="Results" /></td>
</tr>
<tr>
<td>Normal</td>
<td><img src="image5" alt="Results" /></td>
<td><img src="image6" alt="Results" /></td>
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</tbody>
</table>
Galactosaemia screen

- Beutler test
- Pitfalls
  - False positive (false abnormal)
    - Wrong anti-coagulant
    - Old specimen
    - G6PD deficiency
  - False negative (false normal)
    - Transfused blood

- Pitfalls also apply to quantitative enzyme assay
- Allelic variants eg Duarte
Erythrocyte galactose-1-phosphate

- not usually first line test for diagnosis
- remains high after blood transfusion
DNA analysis

- Q188R is a common mutation
  - 70% of cases
- can be tested in transfused patients
- only diagnostic if homozygous
Urine galactitol

- may be helpful in transfused patients
Classical galactosaemia - antenatal diagnosis

- DNA in CVS or amniotic fluid cells
- enzyme activity in CVS cells or cultured amniotic fluid cells
- galactitol in amniotic fluid supernatant
Newborn screening for galactosaemia

How?
- Paigen microbiological method
  - galactose
  - galactose-1 phosphate

Why?
- to prevent mortality
- to start treatment as early as possible
- to improve outcome

BUT
- early presentation
- variants detected
**Classical galactosaemia - treatment**

- **restriction of galactose and lactose**
- **neonate**
  - soya milk
- **older child**
  - avoid hidden sources
  - milk powder, milk solids, hydrolysed whey
  - drugs in tablet form, toothpaste, baking additives, fillers in sausages
  - some cheeses are allowed (Emmenthal, Gruyère, mature Cheddar)
- **vegetables**
  - galactolipids, polysaccharides, disaccharides, oligosaccharides
  - need (bacterial) \( \alpha \)-galactosidase to be broken down
Classical galactosaemia - long term outcome

- poor intellectual function
  - falling IQ with age
- delayed speech development
- introverted personalities
- mild growth retardation
- ovarian dysfunction
  - loss of bone mineral content
  - HRT may be required
FSH in female galactosaemics
Bone density in galactosaemia

- calcium intake
  - diet inherently deficient in calcium
  - calcium supplements are unpalatable
- hormonal factors
  - females at risk of hypergonadotrophic hypogonadism
- role of galactosides
  - galactose residues normally form part of collagen matrix
Cross sectional study of bone density in galactosaemia

- 20 patients, age 5-22 years (11 M, 9 F)
  - 10 pre pubertal, 4 early puberty, 6 late/post pubertal
- Areal bone density is significantly reduced compared to normal
- Volumetric bone density in the majority falls within the normal range for age.
- Growth in galactosaemia may be compromised compared with the normal population.
Bone Density Results

![Graph showing bone density results with z-scores on the y-axis and total bone density and volumetric bone density/BMAD on the x-axis. The graph includes data points for various z-scores ranging from -3 to 0.]
Possible aetiology of problems

- in utero damage
- diet not restrictive enough
- endogenous “self-intoxification”
- deficiency of UDP galactose or complex galactose containing molecules
Classical galactosaemia – treatment issues

- How should we monitor?
  - Galactose-1-phosphate
    - Some endogenous production
    - Toxic concentrations not defined
- Is treatment required for life?
- How should we treat variant cases?
Classical galactosaemia - summary

- May still be under diagnosed
- REM EM BER
- Urine sugars may be unhelpful
- If galactosaemia suspected always do galactosaemia screen on blood
- If baby has had a transfusion please phone to discuss investigation
Galactokinase deficiency
Galactokinase deficiency

- bilateral nuclear cataracts in early infancy
- galactose and galactitol in urine
- enzyme defect in RBC or skin
- incidence approx 1 in 40,000 (Switzerland)
- can use milk/galactose load for diagnosis
Epimerase deficiency
Epimerase

- **Severe form**
  - present like classical galactosaemia
  - treatment difficult
    - patients are galactose dependant

- **Mild form**
  - patients remain healthy
  - no treatment required
Fructose

- fructose - fruits, vegetables, honey
- sorbitol - fruits and vegetables
- sucrose (glucose-fructose)

- site of metabolism
  - 75% liver
  - 20% kidney
  - 10% intestine

- metabolic fate
  - phosphorylated by fructokinase
  - broken down by aldolase B to DHAP & glyceraldehyde-3-P
Inborn errors of fructose metabolism

- fructokinase deficiency (essential fructosuria)
- fructaldolase deficiency (hereditary fructose intolerance)
- fructose-1,6-bisphosphatase deficiency
Essential fructosuria

- fructokinase deficiency
- autosomal recessive
- benign and asymptomatic
- usually incidental finding (positive urine reducing substances)
- rare (approx 1 in 130000)
- liver, intestine, renal cortex
Hereditary fructose intolerance (HFI)

- Aldolase B deficiency
- Key enzyme in fructose metabolism
- Three isoenzymes each with four identical subunits
  - A: muscle
  - B: liver, renal cortex, small intestine
  - C: brain
- Substrates
  - Fructose-1-phosphate
  - Fructose-1,6-bisphosphate
- Aldolase B has highest $V_{max}$ for fructose-1-P
Hereditary fructose intolerance (HFI)

- Symptoms dependent on fructose intake
  - NB sucrose, sorbitol

- Fructose → fructose-1-P
  - High activity of fructokinase
  - Depletion of Pi and ATP

- Hypoglycaemia
  - Inhibition of glycogenolysis
  - Inhibition of gluconeogenesis
Hereditary fructose intolerance (HFI)

- Vomiting is a constant finding
- Acute presentation
  - Sweaty, trembling
  - Nausea, vomiting
  - Lethargy, coma
  - Severe liver and kidney failure
  - Death
Hereditary fructose intolerance (HFI)

- Vomiting is a constant finding
- Chronic presentation – undulating course
  - Poor feeding, vomiting
  - Failure to thrive
  - Hepatomegaly
  - Less commonly
    - Drowsiness, crying, vomiting, haemorrhages, abdominal distension, irritability, diarrhoea
  - Absence of dental caries
Hereditary fructose intolerance

- Laboratory findings
  - Abnormal liver function
  - Post-prandial hypoglycaemia
  - Hypophosphataemia
  - Renal tubular dysfunction

- Diagnosis
  - Urine sugar chromatography
  - Fructose load (measure glucose, PO_4, Mg, urate, HCO_3)
  - **DANGEROUS**
  - DNA mutation analysis
  - Aldolase B measurement (liver)

- Treatment
  - Fructose free diet
  - Sub-optimal control may lead to growth retardation
HFI case 1

- 6 year old boy
- hepatomegaly discovered at routine school medical (10 cm)

PMH
- FTND
- thirsty, sweaty baby
- 1 episode at 6m - difficult to arouse
- consanguineous parents
- diet normal but avoids fruit juices
- stools pale and very bulky

Initial investigations
- normal liver function tests, glucose, lactate, electrolytes
- liver biopsy showed fatty liver and fibrosis
- normal sweat test
HFI case 1

Fructose load (50 ml apple juice = 3.5 g)
symptomatic at 50 mins - pallor, sweatiness, decreased level of consciousness

<table>
<thead>
<tr>
<th>Time</th>
<th>Gluc (mM)</th>
<th>Lact (mM)</th>
<th>PO₄ (mM)</th>
<th>Mg (mM)</th>
<th>urate (mM)</th>
<th>TCO₂ (mM)</th>
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<tbody>
<tr>
<td>0</td>
<td>6.6</td>
<td>2.5</td>
<td>1.33</td>
<td>0.82</td>
<td>255</td>
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<td>2.5</td>
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<td>19.3</td>
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<tr>
<td>60</td>
<td>2.5</td>
<td>2.1</td>
<td>1.32</td>
<td>0.98</td>
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<td>18.6</td>
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<td>1.71</td>
<td>0.68</td>
<td>315</td>
<td>15.4</td>
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</table>
HFI case 1

- DNA - homozygous for the common mutation
- dietary treatment commenced
- ascorbate and folate supplements
HFI case 2

- 18 month boy
  - 8 months weaning problems
  - 9 month vomiting, pallor, unconsciousness following 2 tsp fromage frais
  - Diagnosis made by DNA
  - Maintained on diet
want to relax diet
300mg fructose load
asymptomatic
<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Gluc (mM)</th>
<th>Lact (mM)</th>
<th>PO₄ (mM)</th>
<th>Mg (mM)</th>
<th>urate (µM)</th>
<th>TCO₂ (mM)</th>
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<tr>
<td>0</td>
<td>4.1</td>
<td>2.0</td>
<td>1.47</td>
<td>0.84</td>
<td>281</td>
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<td>15</td>
<td>4.3</td>
<td>0.9</td>
<td>1.39</td>
<td>0.82</td>
<td>298</td>
<td>20.6</td>
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<tr>
<td>30</td>
<td>4.0</td>
<td>2.0</td>
<td>No sample</td>
<td></td>
<td></td>
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<tr>
<td>45</td>
<td>4.0</td>
<td>2.0</td>
<td>1.31</td>
<td>0.89</td>
<td>333</td>
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<td>60</td>
<td>3.9</td>
<td>1.6</td>
<td>1.29</td>
<td>0.86</td>
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<td>22.4</td>
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<td>90</td>
<td>4.0</td>
<td>1.0</td>
<td>1.57</td>
<td>0.98</td>
<td>333</td>
<td>21.4</td>
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<td>120</td>
<td>3.9</td>
<td>1.0</td>
<td>1.66</td>
<td>0.96</td>
<td>324</td>
<td>21.6</td>
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</table>
Fructose-1,6-bisphosphatase deficiency

- Symptoms not dependent on but are exacerbated by fructose ingestion
  - Neonatal
    - Hypoglycaemia
    - Metabolic acidosis and hyperventilation
    - Hepatomegaly
    - Hypotonia
  - Infancy
    - Crises precipitated by fasting or infection
    - Hepatomegaly
    - Weakness
    - Hyperventilation
    - Trembling
    - Lethargy
Fructose-1,6-bisphosphatase deficiency

- Laboratory abnormalities due to impaired gluconeogenesis
  - Hypoglycaemia
  - Lactic acidemia
  - Increased pyruvate
  - Increased alanine
  - Increased uric acid
  - Increased free fatty acids
  - Glycerol and glycerol-3-P in urine

- Hepatic and renal tubular dysfunction rare
Fructose-1,6-bisphosphatase deficiency

SSIEM, 2010 Santos et al, UK cases

25 patients – age at presentation

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Age at presentation</th>
</tr>
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<tbody>
<tr>
<td>9</td>
<td>1-5 days</td>
</tr>
<tr>
<td>12</td>
<td>5 days – 30 months</td>
</tr>
<tr>
<td>1</td>
<td>9 years</td>
</tr>
<tr>
<td>1</td>
<td>pre-symptomatic diagnosis</td>
</tr>
</tbody>
</table>

All had lactic acidaemia and all but one had hypoglycaemia

Treatment

ER +/- uncooked cornstarch

2 died during acute episode
Pentose phosphate pathway

- Provides ribose-5-phosphate for RNA synthesis
- Reduction of NADP to NADPH
Defects of pentose phosphate pathway

- glucose-6-phosphate dehydrogenase deficiency
  - decreased NADPH production in rbc
  - rbc vulnerable to oxidative stress
    - certain drugs must be avoided
  - X-linked disorder
  - may give false positive in Beutler test
Defects of pentose phosphate pathway

- Transaldolase deficiency (TALDO)
  - progressive liver failure and cirrhosis
  - polyols
    - erythritol, arabitol, ribitol

- Ribose-5-phosphate isomerase deficiency
  - one patient, neurological phenotype
  - polyols
    - arabitol, ribitol
Glucose transporters

- Enable transport of hydrophobic monosaccharides across lipophilic cell membrane
- Sodium dependent glucose transporters (SGLTs)
  - Active transport linked to sodium
- Facilitative glucose transporters (GLUTs)
  - Transport along existing gradients
SG LT defects

- **congenital glucose/galactose malabsorption**
  - SG LT1 apical membrane of enterocytes
  - neonatal presentation
    - bloating, profuse watery osmotic diarrhoea
    - severe hypertonic dehydration
    - repeated failure to reestablish oral feeds after PN
    - treat with fructose (absorbed by GLUT5)

- **renal glycosuria**
  - SG LT2 transports glucose but not galactose
  - glycosuria, normoglycaemia, normal renal tubular function
GLUT1

- Early onset epileptic encephalopathy
- Present during 1st year of life
- Developmental delay, complex movement disorder
- DNA shows most cases are heterozygous de novo mutations

Treatment
- Ketogenic diet in childhood
- Avoid GLUT1 inhibitors
- Some AEDs, alcohol, methylxanthines (caffeine, theophylline)
Diagnosis of GLUT1 deficiency

- Low CSF glucose in the presence of normoglycaemia
  - Normal CSF lactate
- Results in 20 patients with GLUT1 deficiency (observed range)
  - Blood glucose: 3.4-9.4 mmol/l
  - CSF glucose: 0.9-2.7 mmol/l
  - CSF/blood glucose ratio: 0.19-0.46
  - CSF lactate: 0.3-1.5 mmol/l

CSF glucose concentrations (mM)

(GLUT1 < 2.7)
csf glucose concentrations (mM)

(GLUT1 < 2.7)
csf/plasma glucose ratio
(GLUT1 < 0.4)
Guidelines for CSF sampling

- Patient preparation
  - Fast overnight
- Take blood first (BEFO RE LP)
  - Glucose, lactate - fluoride oxalate
  - Amino acids – lithium heparin
- Take CSF
  - Glucose, lactate - fluoride oxalate
  - Amino acids – plain bottle
Fanconi-Bickel syndrome (G LUT2)

- infancy (2-10m)
  - hepatomegaly
  - Fanconi-like nephropathy
  - severe glycosuria
  - fasting hypoglycaemia
  - postprandial hyperglycaemia and galactosaemia and galactosuria

- later
  - protuberant abdomen
  - moon shaped face
  - short stature
  - enlarged kidneys
  - hypophataemic rickets
Fanconi-Bickel syndrome (G LUT2)

**G LUT2**

- high $K_m$ monosaccharide transporter (gluc/ gal)
  - hepatocytes
  - proximal renal tubule
  - enterocytes
  - pancreatic $\beta$-cells

**Pathogenesis**

- impaired hepatic uptake of gluc/gal
- impaired insulin response to hypoglycaemia
- gluc not released from liver when hypoglycaemic
- impaired transport in renal cells
- glycogen storage
FBS case

- **Routine biochemical abnormalities**
  - slightly increased transaminases
  - increased lactate
  - urate
  - lipids
  - calculated glucose reabsorption ‘zero’

- **Treatment**
  - symptomatic
  - UCCS
  - electrolyte replacement

- **Long term outcome**
  - major problem is growth
FBS case

- 12 month old boy
  - 6m - cow’s milk intolerance - changed to Soy milk
  - increasing abdominal distension
  - faltering growth
    - 25th to 0.4th centile since 5m

- DGH
  - advanced rickets
  - renal Fanconi syndrome
    - glycosuria, phosphaturia, proteinuria, renal tubular acidosis
    - fasting hypoglycaemia

- Diagnosis confirmed by mutation analysis
FBS case

- Post-prandial hyperglycaemia
- Fasting hypoglycaemia
- Blood collected following lunch and 10g UCCS

<table>
<thead>
<tr>
<th>Hours post lunch</th>
<th>Glucose mM</th>
<th>Lactate mM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.0</td>
<td>2.9</td>
</tr>
<tr>
<td>2 ¼</td>
<td>3.1</td>
<td>1.4</td>
</tr>
<tr>
<td>2 ½</td>
<td>2.9</td>
<td>1.1</td>
</tr>
<tr>
<td>3</td>
<td>2.3</td>
<td>1.0</td>
</tr>
</tbody>
</table>
REAL LIFE DIAGNOSTIC ISSUES

Case examples
Urine reducing substances

- false negatives
- false positives
Urine reducing substances

- false negatives
  - lack of dietary intake
  - dilute urine?
Urine reducing substances

- false positives
  - reducing substances
    - alkaptonuria
  - galactose
    - liver dysfunction
      - tyrosinaemia type 1
  - citrin deficiency
  - Fanconi-Bickel
  - fructose
    - liver dysfunction
Run 2 plates

<table>
<thead>
<tr>
<th>Plate 1 PABA stain</th>
<th>Plate 2 Naphthoresorcinol stain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribose marker</td>
<td>Fructose</td>
</tr>
<tr>
<td>Glucose</td>
<td>Sucrose</td>
</tr>
<tr>
<td>Galactose</td>
<td>Lactulose</td>
</tr>
<tr>
<td>Lactose</td>
<td>Raffinose</td>
</tr>
</tbody>
</table>
Case 1

- female
- FTND 3.2 kg
- no consanguinity
- sister 4 years - well
- 2 days
  - discharged from hospital
  - mild jaundice
Case 1

- days 3-5
  - increasing jaundice noted by midwife
  - bilirubin 452 µmol/l
- day 6
  - readmitted, weight 2.92 kg
  - O/E
    - well
    - no hepatosplenomegaly
  - commenced phototherapy
Case 1

- Bilirubin: 400 µmol/l
- Coombs test: negative
- PT: 94/13
- PTT: 100/37
- Treated with vitamin K
- Urine:
  - Clinitest: 2%
  - Clinistix: neg
- Galactosaemia screen: ABNORMAL
- Commenced dietary treatment
Case 1

- 8 days
  - unwell
  - abdominal distension
  - bleeding
    - PT 120/13
    - PTT 250/39
- treated with IVI, FFP, antibiotics
- home at 17 days
Case 2

- **FTND**: 4.24 kg

- **Day 3**: bilirubin 295 µmol/l
  - Phototherapy commenced
  - Poor feeding
  - Sleepy
  - Possibly ABO incompatibility
  - Coombs and infection screen negative
  - Parents unrelated
  - 5-year-old brother alive and well
Case 2

- **Day 5**: Bilirubin 287 µmol/l
  - Poor intake of food, vomiting

- **Day 6**: Bilirubin 262 µmol/l
  - Vomiting, Dioralyte commenced
  - Urine - reducing substances positive (sucrose and glucose)

- **Day 7**: Bilirubin 369 µmol/l
  - Vomiting when feeds restarted

- **Day 8**: Bilirubin 371 µmol/l
  - Urine result received
  - Feeds restarted
  - Hepatosplenomegaly noted
  - Vomited
  - Bmstix 1, Dioralyte recommenced
Case 2

Day 9

- Bar swallow - no gastric emptying
- ??pyloric stenosis
  - Test feed
    - No vomiting
    - No palpable tumour
- Sleepy, floppy, very slow at feeding
- Large firm liver
- Nil by mouth
  - BM stix 0 SYMPTOMATIC
  - Responded well to iv dextrose
- No acidosis
Case 2

- liver function tests
  - total bilirubin: 286 µmol/l
  - conj bilirubin: 99 µmol/l
  - alk phos: 1711 IU/L
  - Ast: 212 IU/L
  - Alt: 70 IU/L
  - albumin: 31 g/l
  - prolonged PT and PTT
Case 2

Day 12
- galactosaemia screen abnormal
- confirmed by quantitative enzyme measurement
- commenced dietary treatment
Case 3

- A typical request form?
- Clinical details
  - ‘Metabolic screen. Rule out
    - Urea cycle defects
    - Mild organic acid disorder
    - Glycogen storage disease’
Case 3

- Urine screening tests
  - Clinitest: 1 trace, 2 neg
  - Albustix: 2 pos, 1 unsat

- Amino acids
  - Generally increased pattern, prominent thr in 2 specimens

- Organic acids
  - 1 NAD, 2 slightly increased 4-OH-phenyllactate

- GAGS and oligos (2 specs)
  - 2 faint oligo bands in one spec
  - Increased DMB in one spec

- VLCFA, acyl carnitines normal

- Transferrin electrophoresis abnormal

- Amino acids suggestive of liver dysfunction
Case 3

- Follow-up of transferrin electrophoresis
  - Neuraminidase digestion
  - Repeat specimen
    - Confirmed abnormality
  - Galactosaemia screen – ABNORMAL
  - Hereditary fructose intolerance
    - Not tested for
Case 3

- FTND
- 2w – viral illness
  - Abnormal LFTs, palpable liver, resolved over next 2 months
- 4m – projectile vomiting
- 5m – infected eczema
  - LFTs again abnormal, slightly increased TSH, normal fT4
  - Developmental delay, failure to thrive, poor feeding
- 7m – cataracts, macrocephaly
Case 3

- **Galactosaemia screen**
  - ABNORMAL

- **Urine reducing substances**
  - negative

- **Urine sugar chromatography**
  - Trace amounts of galactose on lactose containing feeds from birth
  - Approx 50% more lactose than normal infant
Case 3

- G6PD
  - normal
- Galactose-1-phosphate uridyl transferase
  - undetectable
- Mutation analysis
  - Q188R hetero
- Galactose-1-phosphate
  - grossly increased
Case 4

- born at 29/40 because of placental problems
- well at birth
- 1 week
  - coagulation problems
  - renal failure
  - intraventricular haemorrhage
  - breast fed for 72 hours then on 10% dextrose
Case 4

- neonatal screening results
  - increased phenylalanine, increased tyrosine
  - galactosaemia screen
    - ABNORMAL
  - tyrosinaemia screen
    - EQUIVOCAL

- had had 6 transfusions
Case 4

- no urine obtainable
- DNA analysis
  - Q188R heterozygote
- erythrocyte galactose-1-phosphate
  - grossly increased
- baby died at 23 days
- diagnosis confirmed in fibroblasts
Case 5

- FTND 39/40
- 5 days
  - not feeding well
- 6 days
  - jaundiced
  - handling poorly
  - abdominal distension
- Midwife visit
  - immediately to hospital
Case 5

- Bilirubin: 317 µmol/L (conj 72 µmol/L)
- INR: >10
- Lactate: 17.2 mmol/L
- Ammonia: 266 µmol/L

- Advanced sepsis with DIC
- High inotrope requirement
- Anuric
- Peritoneal dialysis
- Ventilated
- Died at 7 days of age
Case 5

- **Urine**
  - Amino acids grossly increased
    - Renal tubular dysfunction/acute collapse
  - Organic acids
    - Severe liver dysfunction
  - Sugar chromatography
    - Galactose

- **Blood**
  - Acyl carnitines normal
  - Amino acids
    - Grossly abnormal (severe liver dysfunction and acute collapse)
  - Galactosaemia screen normal
  - Tyrosinaemia screen equivocal
Case 5

- post-mortem - cause of death
  - E. coli sepsis
  - peritonitis

- review of results
  - blood transfusion prior to blood specimen
Case 5

- review of results with consultant
  - blood transfusion prior to blood specimen
  - no blood taken for DNA
  - skin biopsy banked

- parents tested for Q188R
  - both heterozygous

- DNA extracted from fibroblasts
  - Q188R homozygote
Case 6

- born at 31/40
- urine for ‘metabolic screen’
  - amino acids - normal
  - organic acids - liver dysfunction
  - positive Clinitest, trace Clinistix
- baby transferred to hospital 2
  - had multiple transfusions for low Hb
- arranged
  - urgent sugar chromatography
  - blood for galactose-1-phosphate
Case 6

- urine sugar chromatography
  - galactose > 10 mmol/l
- erythrocyte galactose-1-phosphate
  - increased
- baby transferred to hospital 3
- DNA
  - Q188R homozygote
- baby transferred to hospital 4 for treatment
Case 7

- 3w old boy
  - prolonged jaundice bilirubin 295 µmol/l
- galactosaemia screen abnormal
- further information
  - feeding well
  - gaining weight
  - normal liver enzymes
  - no reducing substances in urine
Case 7

- Repeat blood obtained
  - Galactosaemia screen abnormal
  - Galactose-1-phosphate undetectable
  - Glucose-6-phosphate dehydrogenase undetectable

- Filipino mum
Case 8

- Baby of galactosaemic father tested at birth
  - Multi-consanguineous family
  - GALT mutation + Duarte 2 mutation
  - Galactosaemia screen abnormal/equivocal
  - Galactose-1-phosphate grossly increased
  - Commenced on diet

- Over the next few months
  - Galactose-1-phosphate undetectable – twice
  - DNA showed heterozygous for family mutation & Duarte 2
Case 8

- 1 year
  - galactose-1-phosphate increased
  - more DNA results
  - compound heterozygote for 2 GALT mutations
  - also has Duarte 1 and Duarte 2
  - GAL1PUT activity 2.0 µmol/h/g Hb
  - VARIANT form of galactosaemia

- maintained on diet
  - when should diet be stopped?