Paediatric Metabolic Disorders

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100 years in child health

- For centuries, “childhood deaths were inevitable”
- families → loss of half (or more) of their children.
- Seemingly nothing could be done
- “nature take its course”
100 years in child health

• For centuries, “childhood deaths were inevitable”
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Infectious Diseases Mortality
Paediatric mortality – progress in infectious diseases

• Social intervention
  – hygiene, improved living conditions, sanitation, housing and employment.
• Infectious gastroenteritis, Smallpox, HIV
• Vaccination
• Breast feeding
Paediatric mortality – progress in non-infectious diseases

- congenital heart disease
- acute leukaemias
- functional asplenia sickle cell disease,
- legal redress for the battered child,
- prone sleeping position and SIDS
Paediatric mortality – advanced Dx of metabolic disorders

• Newborn screening
• designed to save babies from death or irreversible harm by detecting rare diseases quickly.
• NBS has changed infant health
  – 12 000 babies a year saved or life improved

* According report by the Association of Public Health Laboratories (USA 2013)
But …

• > 60% of inborn errors or metabolic disorders occur outside the newborn period
• despite advancements in technology, laboratory scientists will be faced with laboratory abnormalities in a child
  – acute metabolic acidosis,
  – hyperammonaemia,
  – hypoglycaemia,
  – hyperbilirubinaemia and acute liver failure.
But …

• > 60% of inborn errors or metabolic disorders occur outside the newborn period
• despite advancements in technology, laboratory scientists will be faced with laboratory abnormalities in a child
  – acute metabolic acidosis,
  – hyperammonaemia,
  – **hypoglycaemia**,
  – hyperbilirubinemia and acute liver failure.
Definition of neonatal hypoglycaemia

• plasma glucose < 2.6 mmol/L
• a “practical working definition”

• Note: infants can have symptoms of hypoglycaemia at glucose levels > 2.6 mmol/L and require treatment, but this is unusual.
Essential Diagnostic Sample

- to be collected on child during hypoglycaemic episode
- plasma glucose < 2.6 mmol/L
- serum for GH, cortisol, insulin, bOHB, free FA, lactate, plasma NH3, amino acids and acylcarnitines.
- Urine ketones, reducing substances (galactose), organic acids (urine metabolic screen) and urine drug screen.
Paediatric hypoglycaemia by age

NEWBORN  NEONATAL  INFANT
birth    7 days  2 weeks  1 month  6 months  12 months  5 years

1. Persistent Hyperinsulinism
2. Endocrine disorders
3. Inborn error of metabolism

Transient hypoglycaemia

Idiopathic ketotic hypoglycaemia
Hypoglycaemia in newborns

Transient

- SGA/ LBW
- Preterm
- Stress at delivery
- Maternal diabetes
- Neonatal illness (infection, hypothermia)

Persistent

- Inborn error of metabolism
Case-1

• Your lab is called about a baby born at term. Infant is 8h of age and reported to have poor feeding and hypothermia.

• Lab plasma glucose was 1.4 mmol/L.
• What are the most likely causes?
Neonatal hypoglycaemia is common

- Hypoglycaemia is more common during the first days after birth than at any other time of life.
- A transient phenomenon in the majority of the cases.
- Immature enzyme function in otherwise normal neonate.
- Inadequate back-up mechanisms to counteract hypoglycaemia.
- Consider events related to gestation.
1. Is it transient hypoglycaemia of newborn?

- Low birth weight (eg. 1800 g)
- Small for gestational age
- Stress
- IDM (large or small for gestational age)
- sepsis
- asphyxia
- prematurity
IDM - infant of diabetic mother

• Prolonged maternal hyperglycaemia → foetal hyperglycaemia → foetus produces high levels of insulin and GH (maternal GH and insulin do not cross placenta). Hyperinsulinaemia persists for 24h after birth increasing the risk of hypoglycaemia.

• macrosomia (large for gestational age)
Hypoglycaemia in newborns

**Transient**
- SGA/ LBW
- Preterm
- Stress at delivery
- Maternal diabetes
- Neonatal illness (infection, hypothermia)

**Persistent**
- Inborn error of metabolism
2. Is it a “persistent hypoglycaemia of newborn”?

- May also have hepatomegaly
- neonatal IEM
  - Galactosaemia
  - Fructosaemia, HFI
  - Glycerol kinase deficiency
  - Tyrosinaemia
  - Glycogen Storage Disease 1

Hypoglycaemia > 2 days
3. Is it persistent hypoglycaemia of infancy?

• same as causes of newborn hypoglycaemia
• Plus:
  – Hyperinsulinism
  – Endocrine disorders
Case-2

- Female aged 7 months presenting with a “bit of gastro”
- Plasma glucose: 0.3 mmol/L
- Insulin: elevated 61 pmol/L
- Cortisol: > 1000 nmol/L
- GH: 20.9 nmol/L
- Blood glucose and insulin study over 10h - insulin levels were not suppressed by hypoglycaemia.
- Initial Dx: PHHI

Persistent hyperinsulinaemic hypoglycaemia of infancy
Case-2 follow up

• Transferrin isoform studies
• Abnormal pattern consistent with CDG (Congenital Disorders of Glycosylation type 1)
• CDG type 1 – there is a defect in synthesis of mannose
Hypoglycaemic Endocrine Disorders

• Addison’s or other adrenal insufficiency
  – Congenital or acquired bilateral adrenal haemorrhage

• Hypopituitarism
  – GH deficiency +/- ACTH deficiency
  – Midline facial defect (cleft lip, and palate)
  – Males may have hypoplastic external genitalia and micropenis.
Endocrine hypoglycaemia

• Most important laboratory findings
  – Low plasma GH in presence of hypoglycaemia
  – short synacthen test showed low basal cortisol and no rise after synacthen
Inborn error of metabolism

- Galactosaemia
- Fructose 1,6 diphosphatase deficiency
- Hereditary fructose intolerance
- Tyrosinaemia
- Glycogen storage disorders
  - GSD1
  - GSD3
- FA oxidation defects (MCAD, Reyes, VLCAD)
- Organic aciduria (Methyl malonic aciduria)
- Aminoacidopathy (Maple syrup urine disease).
Prevalence of the IEMs which present with paediatric hypoglycaemia


<table>
<thead>
<tr>
<th>Condition</th>
<th>Estimated prevalence</th>
<th>References</th>
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<tr>
<td>Medium chain acyl-co dehydrogenase deficiency</td>
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<td>Hydroxyl acyl-CoA dehydrogenase deficiency</td>
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<td>Primary carnitine deficiency</td>
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<td>Citrin deficiency</td>
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<td>Glycogen storage disease IX</td>
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<td>Pyruvate carboxylase deficiency</td>
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<td>Phosphoenolpyruvate carboxylase deficiency</td>
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<td>Fructose 1,6-bisphosphatase deficiency</td>
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<td>Propionic acidemia</td>
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<td>Methylmalonic aciduria</td>
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<td>Maple syrup urine disease</td>
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<td>Galactosaemia</td>
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<tr>
<td>Glycerol kinase deficiency</td>
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HYPOGLYCAEMIA BY BIOCHEMICAL PATHWAYS
Hypoglycaemia by biochemical pathway

1. **glycogenolysis**
2. **gluconeogenesis**
   - Affecting availability and source of substrates
   - Affecting critical enzymes
3. **fatty acid oxidation and ketosis**
   - Disorders of FAO impair production of ketones as an alternate source of fuel (to glucose).
Glycogenolysis - GSD

- GSD type I (von Gierke’s disease)
  - the commonest GSD causing hypoglycaemia.
- Deficiency of glucose-6-phosphatase
- glucose-6-phosphate $\rightarrow$ glucose
- glucose-6-phosphate accumulation
- glycogen stores accumulate $\rightarrow$ marked hepatomegaly.
Hypoglycaemia by biochemical pathway

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Block in gluconeogenesis

• Gluconeogenesis involves 4 enzymes
  – pyruvate carboxylase
  – phosphoenolpyruvate carboxykinase
  – fructose-1,6-diphosphatase
  – glucose-6-phosphatase
• Pyruvate as a precursor
• Gluconeogenic substrates:
  – Amino acids (esp. alanine) from muscle breakdown
  – Glycerol
  – Lactate
Substrates for gluconeogenesis

- All exogenous carbohydrates are converted to glucose for generation of energy.
  - Fructose
  - Galactose
  - Lactose
  - Sucrose
  - Starch

- Disorders where there is inability to utilise dietary COH → hypoglycaemia.

- *Galactosaemia can cause hypoglycaemia*
Case - 3

- Baby girl delivered 38+6 weeks Auburn Hospital
- No complications
- Parents are second cousins
- Discharged home on day 2
- Returned on Day 4 serum BR 408 umol/L.
  Started on phototherapy
- Noted to be lethargic and vomiting after feed.
- Abnormal LFTs
- NBS result → Galactosaemia
Galactosaemia

- deficiency of galactose-1-phosphate uridyl transferase (GALT) 1:47,000
- Lactose →
  - glucose available for immediate supply of energy
  - galactose which requires conversion into glucose (ensures prolonged carbohydrate availability).
- toxic accumulation of galactose-1-phosphate → hepatic impairment, hepatomegaly, hypoglycaemia with ketones
- predisposition to sepsis, esp. caused by Escherichia coli.
- Hypoglycaemia is usually only seen once liver impairment has developed.
Galactose metabolism in healthy individuals.

(1) Intestinal lactase, (2) Galactokinase (GALK), (3) Galactose-1-phosphateuridyltransferase (GALT), (4) UDP-galactose-1,4-epimerase (GALE).
Hypoglycaemia by biochemical pathway

1. glycogenolysis
2. gluconeogenesis
   - Affecting availability and source of substrates
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   - Disorders of FAO impair production of ketones as an alternate source of fuel (to glucose).
Ketogenesis and FAO

• May present with hypoglycaemia
  – Aminoaciduria  MSUD
  – Organic acidaemia  MMA, IVA, PA
  – FA oxidation disorder  CPT, MCAD

• Note:
  – FAOD – hypoketotic hypoglycaemia
  – MSUD and MMA – ketotic hypoglycaemia
Case - 4

- Female aged 6 months
- Sudden onset vomiting, dehydration and loss of consciousness
- pH 7.44, pCO2 26, HCO3 18
- Plasma glucose **1.0** mmol/L
- BR < 10 umol/L, NH3 **101** umol/L

- Conclusion: hyperammonaemia with hypoglycaemia
- Urine metabolic screen
- Dx: MCAD deficiency
MCAD (Fatty Acid Oxidation Disorder)

• disorder of fatty acid oxidation
• Unable to break down fat during periods of fasting.
• commonest mitochondrial FAOD
• 1/10 000 (similar to PKU)
• Have only limited production of ketone bodies from FFA → prone to hypoglycaemia when glycogen reserves are depleted, eg. after a prolonged fast or with inadequate intake (e.g. during an intercurrent illness).
Variable age at presentation

- Classically present with hypoglycaemia during a mild intercurrent illness, (between 3 months - 3 yr).
- The hypoglycaemia can be severe, causing seizures. At other times, they are usually asymptomatic.
- In the 1990s, 22% of children presenting with MCAD deficiency died.
- MCAD is in Australian newborn screening programmes - octanoylcarnitine in blood spots.
Hypoglycaemia in children > 1 year

- Ketotic hypoglycaemia
  - Most common cause of hypoglycaemia in > 12 month old
  - Occurs between 12 months and 5 years
  - Develop hypoglycaemia and ketosis when COH restriction

- Toxins
  - ETOH
  - Insulin/ oral hypoglycaemics
  - Salicylates
  - propranolol

- Liver failure

- Septicaemia

- Tumour burden
Summary paediatric hypoglycaemia

• Definition: plasma glucose < 2.6 mmol/L
• “hypoglycaemia” is more common in paediatrics compared to adult medicine.
• Acquired causes - systemic illness, sepsis, medications, and poor nutritional status.
• Hypopituitarism and adrenal insufficiency should be excluded.
• Might be first presentation of an inborn error of metabolism
Conclusion

• “… the best place to begin a healthy life is at the beginning…”

• Tomorrow: premier research needed
  – foetal programming, foetal maternal interface, genetic testing.
  – treatment of birth defects and chronic illnesses.

• **Laboratory has central role:**
  – gather information, assure quality or results and provide education.

*Thank you*