

Approach to paediatric hypoglycaemia

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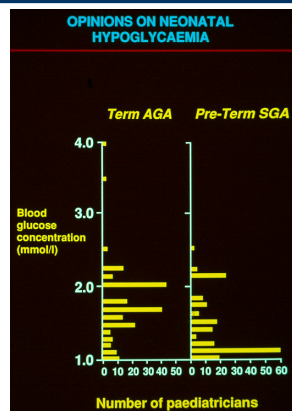
Approach to paediatric hypoglycaemia Outline

- Why begin with hypoglycaemia?
- What is it?
- Why is it important?
- The maintenance of glucose homeostasis
- The investigation of hypoglycaemia
- Disorders causing hypoglycaemia
- Some examples
- Problems
- Conclusions

Why begin with hypoglycaemia?

- It is a relatively common childhood symptom
- It is important in itself but also as a pointer to other conditions
- Not only is it a feature in many IMD's but also the organisation of our response is similar:
 - Awareness
 - Collection of samples when symptomatic
 - An organised and timely approach to analysis
 - A planned approach to appropriate treatment
 - Common illnesses may result in the disturbance

What is it? Opinions on hypoglycaemia



Paediatricians, Koh et al 1988

Glucose value used in neonates to define hypoglycaemia

- <1.7 mmol/L 10%
- <2.2 mmol/L 66%
- <2.8 mmol/L 24%

Paediatricians, Stanley 2006

What is hypoglycaemia?

- No evidence that glucose requirements in neonates differ from those of older children
- Supported by long term outcome studies and neurophysiological sensory evoked potential evidence, it is generally accepted that the concentration must fall below 2.5mmol/L before the patient is symptomatic, although 2.2 mmol/L is often taken as a practical action cut-off in neonates
- Lower in the first 24 hours

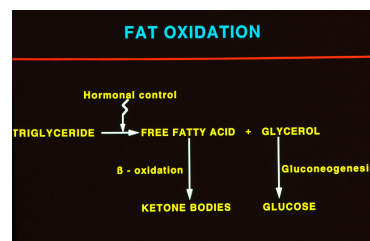
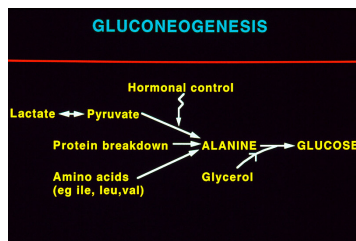
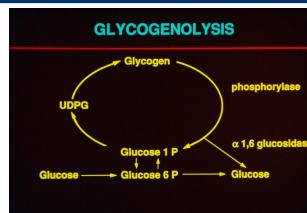
Brain energy metabolism and the effects of hypoglycaemia

- The brain is an extremely metabolically active organ with little endogenous energy storage
- Glucose transport across the BB barrier is facilitated by the GLUT1 receptor and defects are known
- The brain can use ketone bodies as an alternative energy supply
- It can also use lactate and brain lactate levels are 4-5x circulating concentration, derived from glycogen stores in astrocytes
- Damage in white matter is due to breakdown of the Na⁺ gradient and Ca⁺⁺ accumulation
- Damage in grey matter appears to be due to glutaminergic effects
- Glucose is also needed for structural roles in myelin formation and hypoglycaemia during periods of rapid brain growth in the first year of life may result in reduced myelination or atrophy

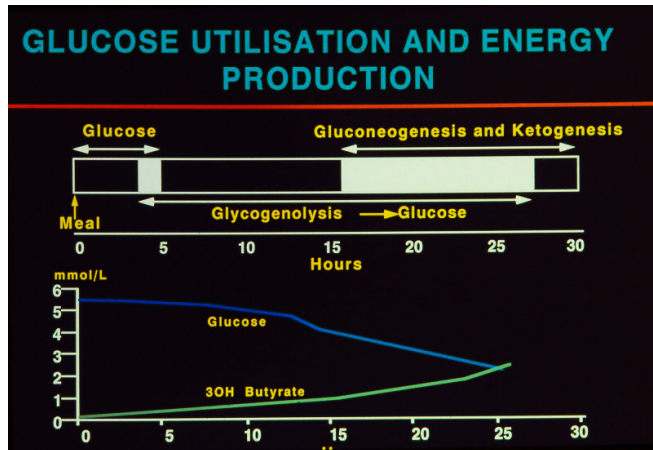
Why is it important?

- It is **“one of the most common metabolic and endocrine abnormalities in infancy and childhood”**
- It directly affects brain function
 - In adults, while the brain accounts for only 2% of body weight it uses 20% of resting energy
 - In children the situation is even more dramatic, the brain of a newborn accounts for 10% of body weight and uses 50% of BMR
- **Persistent or recurrent neonatal hypoglycaemia can have lasting effects**
 - Impairs cerebral growth as reflected in head circumference, *Duvanel et al J Pediatr 1999 134: 492-498*
 - Results in lower developmental scores, Stenninger et al, *Arch Dis Child Fetal Neonatal Ed 1998 79: F174-179*
 - Glucose <2.6 mmol/L results in developmental delay at 18 mo of age, even in asymptomatic cases *Lucas et al, BMJ 1988 297:1304-8*
 - In a series of 90 PHHI cases, 8% severe mental retardation, 18% intermediate retardation, 6% epilepsy, 8% microcephaly. *Menni et al Pediatr 2001 107:476-9*

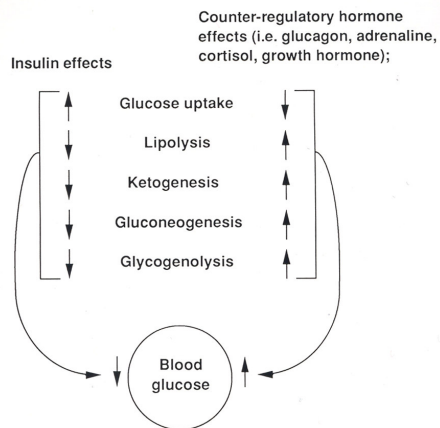
The investigation of hypoglycaemia - glucose homeostasis



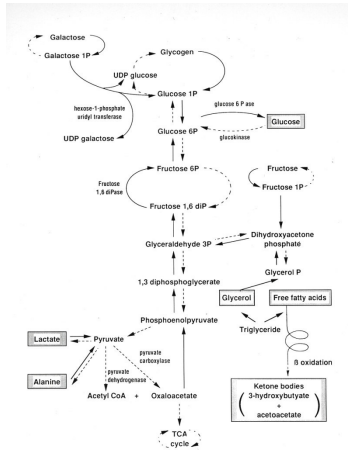
Maintenance of glucose homeostasis



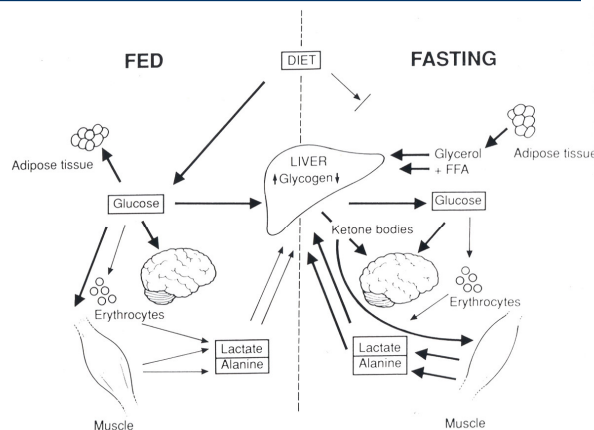
Maintenance of glucose homeostasis



Maintenance of glucose homeostasis



Maintenance of glucose homeostasis



Classification of hypoglycaemia

- **Hypoketosis**

- **Increased glucose utilisation, FFA** ↓
hyperinsulinism (PHHI, transient, SCHAD defn, glutamate dehydrogenase overactivity); large tumours
- **Normal glucose utilisation, FFA** ↑
fat oxidation defects eg MCAD, LCHAD etc

Classification of hypoglycaemia

- **Ketotic**

- **increased lactate**
GSD1, fructose 1:6 diPase, PC def, PEPCK def, organic acidaemias, PDH def
- **normal lactate**
GSD VI, GSD IX, GSD III, GSD IV, GSD 0, hypopituitarism, GH def, cortisol defn, glucagon def, organic acidaemia, idiopathic ketotic hypoglycaemia

Hepatocellular failure

- Neonatal hepatitis, hereditary fructose intolerance, galactosaemia, tyrosinaemia, citrin deficiency

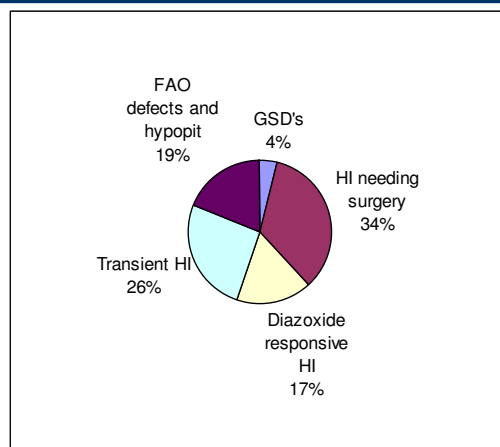
Protocol for the investigation of hypoglycaemia

- Background
 - Either a prolonged fast (can be dangerous)
 - Or, samples taken when the child is hypoglycaemia
- Samples required
 - 2 mL heparin blood: U/E, urate, LFT's, insulin, c-peptide, cortisol, GH, plasma acyl carnitine
 - 2 mL fluoride blood: glucose, FFA, lactate, 3-hydroxybutyrate, alanine
 - 5 mL random urine: organic acids
 - CSF: glucose if GLUT1 is suspected

The use of hypopacs

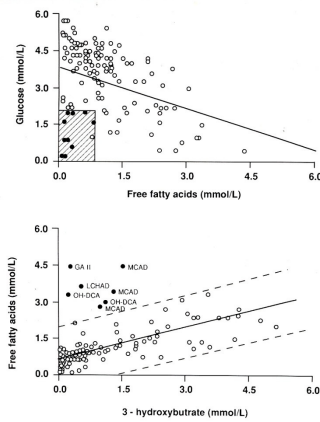
- Packs containing specimen tubes and request forms to be used in conjunction with an agreed protocol
- Example of use in Northern Ireland, *Lang TF et al Ann Clin Biochem 2008 45:486-8*
- Reduced the number treated before samples from 30% to 17%, reduced the number with some samples missing from 33% to 18%, reduced the number with glucose >5 mmol/L 16% to 4%
- From 100 cases investigated
 - 1 MCAD
 - 3 hyperinsulinism
 - 1 ACTH deficiency

What do we find in neonates?



Stanley, Ped Endocrin Rev, 2006:4, Suppl 1 76-81

What do we find?



Examples in practice

- Newborn male, hypoglycaemic from birth. Glucose utilisation rate 14mg/kg/min
- Glucose 1.3 mmol/L
- Lactate 2.4 mmol/L
- Free fatty acids 0.1 mmol/L
- 3-hydroxybutyrate 0.06 mmol/L
- Alanine 379 μ mol/L
- Insulin 106 mU/L when glucose 1.4 mmol/L

Examples in practice

- 3 year old female, 3 convulsions 6 weeks previously.
- 6 days before admission, restless, unwell and off colour. On the day of admission not rousable and unresponsive. Taken to hospital, seizure and remained unconscious for 24h
- Miserable, afebrile, weight 50th centile, length 50-90th centile, no other abnormalities

Examples in practice

• Glucose	1.2	mmol/L
Lactate	1.3	mmol/L
Free fatty acids	1.2	mmol/L
3-hydroxybutyrate	3.7	mmol/L
Alanine	90	µmol/L
Carnitine	24	µmol/L

Examples in practice

- Cortisol <math><10 \mu\text{mol/L}</math>
ACTH 963 ng/L
Synacthen no response
TFT's normal
- Isolated glucocorticoid deficiency, treated with 5 mg hydrocortisone bd. Renin/aldosterone, normal

Points to note

- There are a number of children with recurrent hypoglycaemic episodes who cannot easily be classified, perhaps GSD is under investigated
- Notwithstanding this, idiopathic ketotic hypoglycaemia (accelerated starvation) seems to be alive and well!
- Low glucose with low FFA's is very common in VLBW babies, ? transient hyperinsulinism

Points to note

- The cortisol response in young infants is very poor (*Crofton et al, 2004*) – hypo and nonhypoglycaemic infants <3mo was 205 nmol/L and 116 nmol/L respectively, 50 nmol/L in a newborn is not unusual
- Lactate and alanine is elevated in transient hyperinsulinism – lactate typically 6.0 mmol/L, alanine >500 µmol/L
- Ketonaemia and ketonuria occur in FAO defects eg ketones up to 2.5 mmol/L
- Falsely high (and low) glucose results can be obtained at the bedside
- Fasting can be useful and safe, Morris et al 1996, 138 children over a 2.5 y period

Conclusions

- Hypoglycaemia in children is common
- It can cause serious problems if unrecognised
- Context is important
- It is important to document hypoglycaemia in the laboratory
- Planned investigations and good organisation is essential
- Prompt action and advice can avoid long term problems