Neonatal Hypoglycaemia

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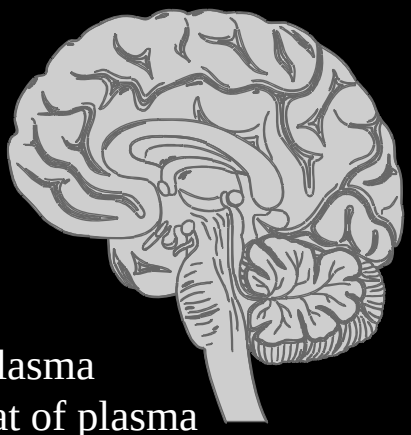
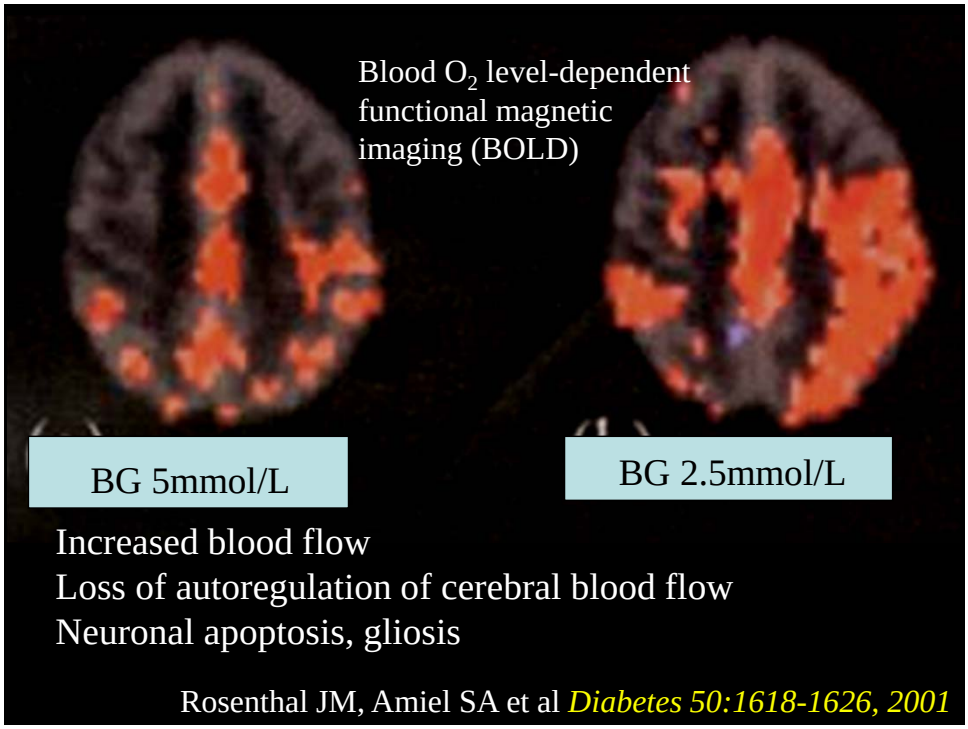
Hypoglycaemia and the Brain



CSF glucose is 2/3 that of plasma
Intracerebral glucose 1/3 that of plasma
Brain has no glucose stores



Increased blood flow
Loss of autoregulation of cerebral blood flow
Neuronal apoptosis, gliosis

Rosenthal JM, Amiel SA et al *Diabetes 50:1618-1626, 2001*

Postnatal glucose metabolism

- Birth → abrupt cessation of glucose supply from maternal-placental source
  - replaced by hepatic glucose production
  - augmented by increased secretion of glucagon, glucocorticoids, catecholamines
- By about 2 hours of age, plasma glucose levels decline to approximately 2.8mmol/L, equilibrating to about 3.5mmol/L by 72 hours of age.
- glucose utilisation
  - term neonates 4-6 mg/kg/min
  - prem neonates 8-9 mg/kg/min

Complications of hypoglycaemia

- Severe glucose deficiency can lead to cerebral energy failure, impaired cardiac performance, muscle weakness, glycogen depletion, diminished glucose production
- Recurrent hypoglycaemia in IUGR babies associated with smaller head circumference and lower psychometric scores at 5 years

Duvanel J Pediatr 1999

- Severe protracted hypoglycaemia with neurological complications such as seizures/ coma associated with learning disabilities, cerebral palsy, recurrent seizures
  - ? due to hypoglycaemia or neurological complication
- No evidence that transient asymptomatic neonatal hypoglycaemia associated with adverse outcome

Luca, now age 14 months

- Pregnancy complicated by maternal hypertension requiring hydralazine and nifedipine
- Born at 35 weeks gestation BW 3478g (99th)
- Apgars 6^{1} 9^{5}
- jittery at 1.5 hours age - BG 1.1mmol/L,
- given feed – BG 2.2mmol/L (confirmed on formal BG)

Luca – initial thoughts?

- Is his BG abnormal?
- Does he have risk factors for neonatal hypoglycaemia?
- Investigations?
- Initial mangement?

Neonatal hypoglycaemia - definition

- No research basis or consensus regarding the definition of neonatal hypoglycaemia
  - <72 hours BG< 2.2 mmol/L , >72 hours BG < 2.6mmol/L
  - <24 hours BG <1.7mmol/L, >24 hours BG <2.5mmol/L
  - “mild” <3.3mmol/L, “moderate” <2.2mmol/L, “severe” <1.1mmol/L
  - operational threshold – BG concentration at which one should consider intervention
  - clinical definition – BG associated with clinical signs that resolve when glucose administered
  - ? no evidence to support that newborn has unique adaptation to low BG levels, therefore hypo = BG<3.9mmol/L

Risk factors for neonatal hypoglycaemia

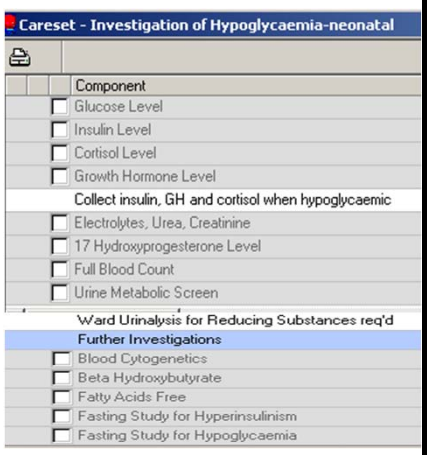
- Normal glucose levels may not be maintained in some infants due to:
  - maternal conditions
    - hyperglycaemia, hypertension, beta blocker medication, substance abuse
  - neonatal conditions
    - lack of glycogen stores due to prematurity and/or growth retardation
    - polycythaemia, Rhesus disease
    - excessive utilisation of glycogen stores due to asphyxia or hypothermia
    - hypermetabolic state due to hypo- or hyperthermia, sepsis
    - inadequate substrate due to starvation, vomiting
    - endocrine and metabolic disorders

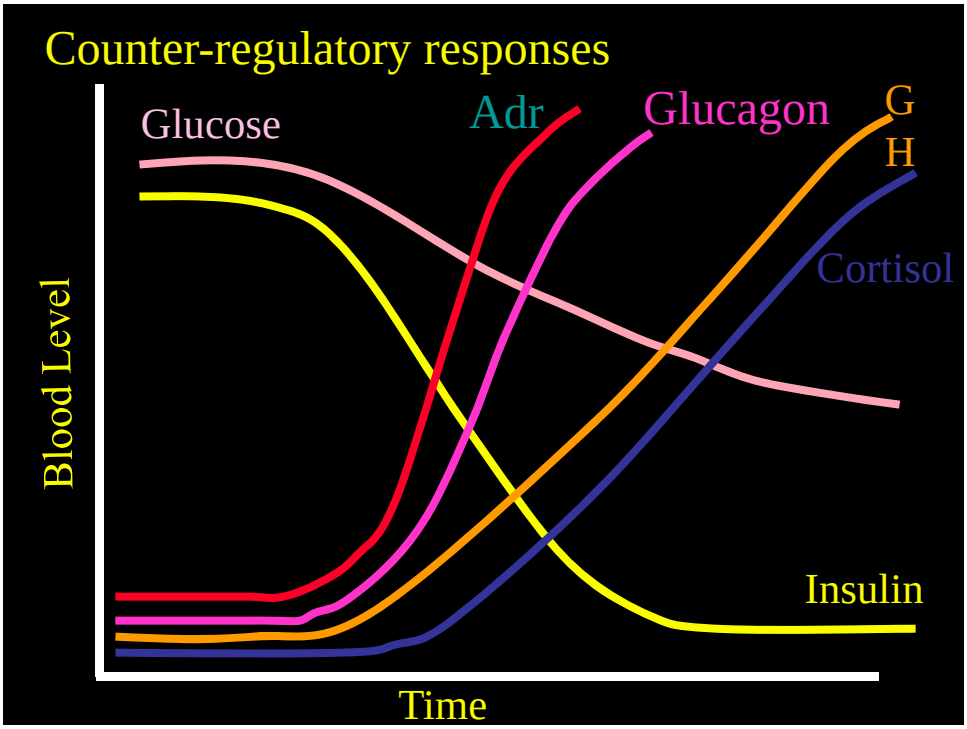
Luca – early management

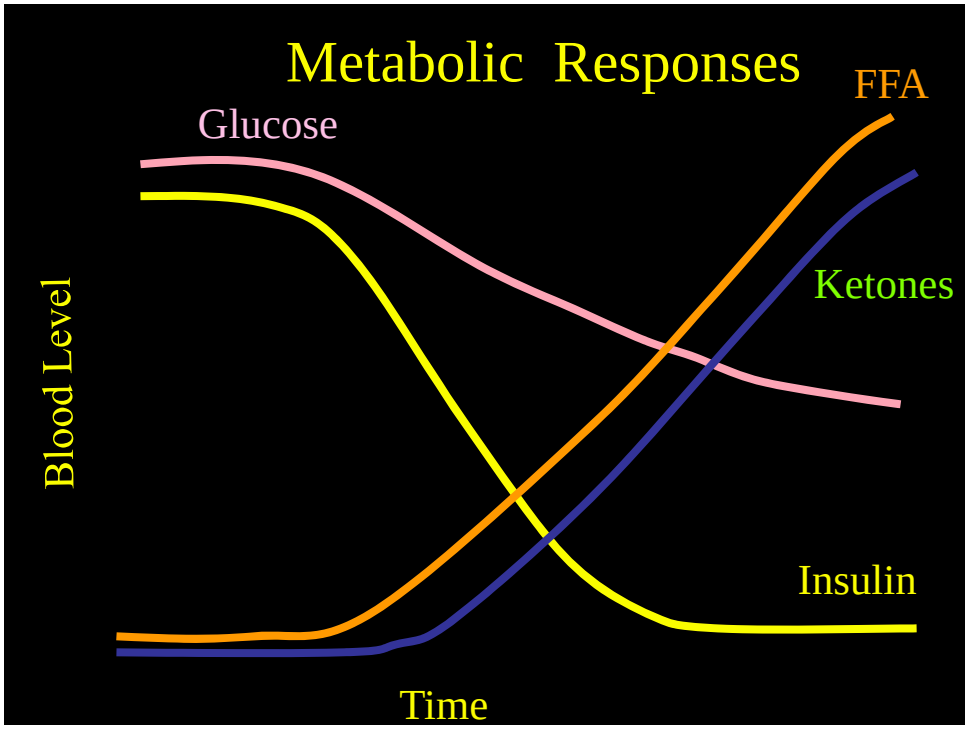
- Given N/4 + 10% dextrose IV at 5ml/hr(D=2.4mg/kg/min)
  - BG 1.8, 2.0 mmol/L
- Full feeds – breast/bottle+IGT top-ups (polyjoule added -28kcal/30ml → osmotic diarrhoea)
- Dextrose infusion increased to N/4 + 12.5%D at 12ml/hr (D=7mg/kg/min) + full enteral feeds
  - maximum BG 3.6mmol/L, most <3.0mmol/L
- Insulin 0.2mU/L (=1.2pmol/L) BG 2.2 mmol/L 2 hours previously ie not really paired?
- Ongoing hypos to 1.7mmol/L
- Transferred to CHW for further investigation and management

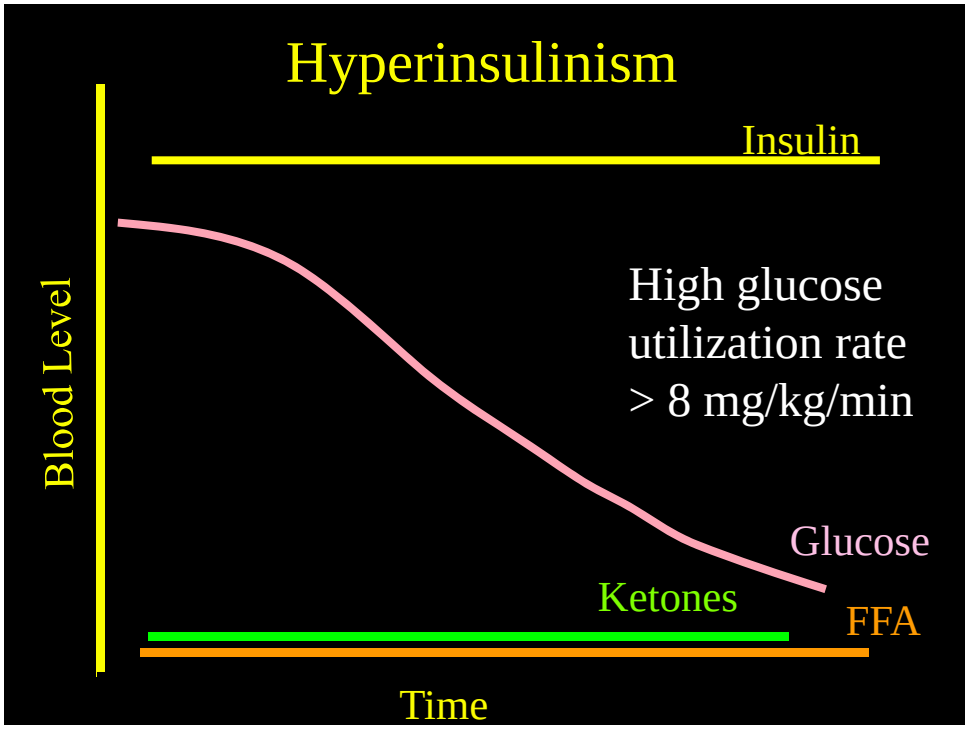
Luca - investigations

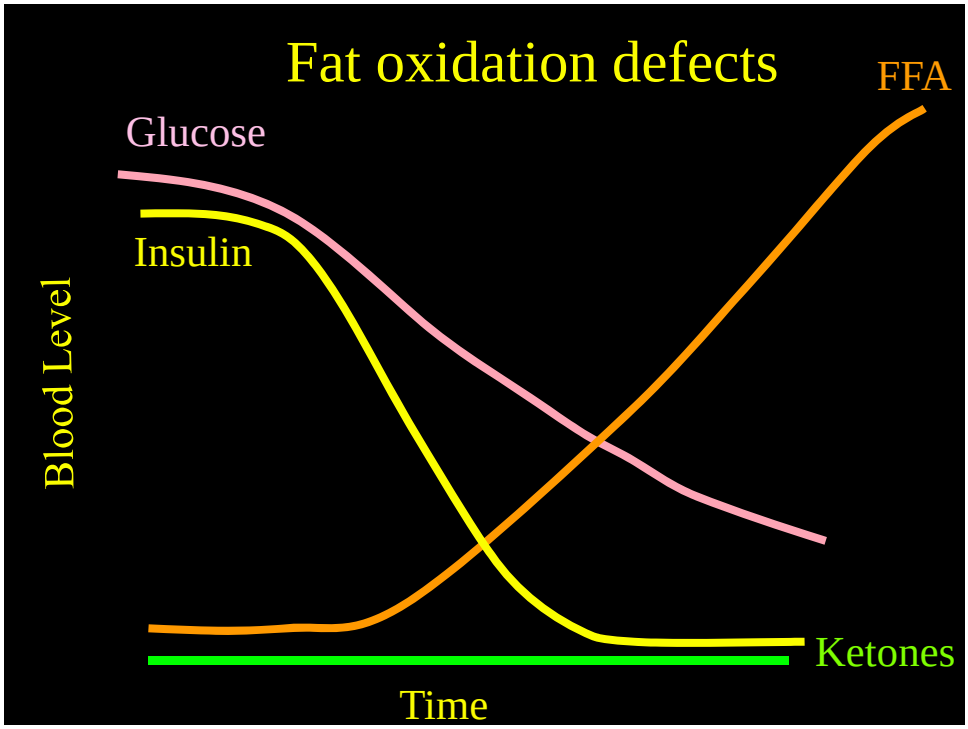
- On arrival BG 2mmol/L
- Critical samples taken
  - 5.5ml blood
    - LiHep 2x2ml
    - Fl Ox 1x1ml
    - 0.5ml blood gas
      bedside ketones
  - 10-20ml urine
    - Reducing substances
    - Metabolic screen











Condition	G	Ins	FFA	KB	GH	Cortisol
Normal	N	L	H	H	N	N
HI	L	H	L	L	H	H
FatOx d	L	L	H	L	H	H
Ketotic	L	L	H	H	H	H
Hypopit	L	L	H	H	L	L
Adrenal	L	L	H	H	H	L

Hypoglycaemia - Case 1

Infant 3 months of age. Poor intake for 2 days. Early morning convulsion. BG 1.3 mM

Previous history and examination unremarkable

Investigations
BSL 1.3 mM, Insulin 6 mU/L
FFA 0.3 mM, β-Hydroxy-butyrate 0.2 mM
Urine metabolic screen normal
Cortisol 765 nM, GH 23 mU/L

Diagnosis: Hypoglycaemia, low FFA, low ketones,

Hyperinsulinism

Hypoglycaemia - Case 2

Infant 3 months of age. Poor intake for 2 days. Early morning convulsion. BG 1.3 mM

Previous history and examination unremarkable

Investigations
BSL 1.3 mM, Insulin < 2 mU/L
FFA 2.8 mM, β-Hydroxy-butyrate 2.1 mM
Urine metabolic screen normal
Cortisol 65 nM, GH < 2 mU/L

Diagnosis: Hypoglycaemia, high FFA, high ketones
low cortisol, low GH
Hypopituitarism

Hypoglycaemia - Case 3

Infant 3 months of age. Poor intake for 2 days. Early morning convulsion. BG 1.3 mM

Previous history and examination unremarkable

Investigations
BSL 1.3 mM, Insulin < 2 mU/L,
FFA 2.8 mM, β-Hydroxy-butyrate 0.15 mM,
Urine metabolic screen high C6-C10 dicarboxylic acids
Cortisol 765 nM, GH 23 mU/L,

Diagnosis: Hypoglycaemia, high FFA, low ketones
Fatty acid oxidation defect

Luca - management

- Persistent hypoglycaemia on IV fluids + feeds
- Glucose requirement 14mg/kg/min
- Commenced on glucagon 10 mcg/kg/hour, increased to 20mcg/kg/hr
- Diaxozide 5mg/kg/day increased to 10 mg/kg/day (8 hourly dose)
- Hydrochlorothiazide added (2mg/kg/day)
  - Na and K losses
- Polyjoule added to feeds – osmotic diarrhoea and skin excoriation

Luca - results

- BG 2 mmol/L
  - GH 13.4 mU/L, 20.4mU/L
  - Cortisol 381nmol/L
    - Synacthen stimulation test: peak 1073 nmol/L
  - Insulin 60 pmol/L
  - Ketones negative
  - FFAs 0.3 mmol/L (low)

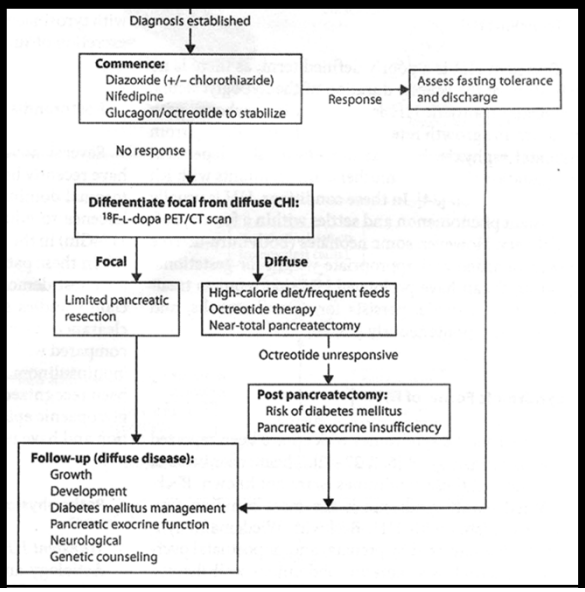
Luca – further results

- Urine metabolic screen normal
- Transferring isoforms normal
- Ammonia 41umol/L (normal)
- Abdo ultrasound - normal pancreas

Luca – ongoing management

- Discharged home on diazoxide 7.5mg/kg/day
- Thiazide ceased
- Ongoing diazoxide requirement of 10mg/kg/day despite good intake of solids
- Displaying age appropriate development
- Considering genetic testing for focal vs diffuse hyperinsulinism, genetic counselling for future pregnancies

Hyperinsulinism treatment



Hussain, *Horm Res:* 2008 p2

Hyperinsulinism, medical therapy

Table 2. Summary of the medications used in the treatment of CHI: their doses, side effects, and the possible mechanisms of action

Medication	Route of administration	Dose	Mechanism of action	Side effects
Diazoxide	Oral	5–20 mg/kg/day divided into 3 doses	Agonist of the K_{ATP} channel	Common: fluid retention, hypertrichosis Uncommon: hyperuricaemia, eosinophilia, leukopaenia, rarely hypotension
Chlorothiazide (used in conjunction with diazoxide)	Oral	7–10 mg/kg/day divided into 2 doses	Activation of K_{ATP} channels Synergistic response with diazoxide	Hyponatraemia, hypokalaemia
Nifedipine	Oral	0.25–2.5 mg/kg/day divided into 3 doses	Calcium channel blocker	Hypotension (uncommon)
Glucagon (+/– octreotide)	s.c./i.v. infusion	1–20 μg/kg/h	Activates adenylate cyclase via the G-protein-coupled receptor (G_s), increases glycogenolysis and gluconeogenesis	Nausea, vomiting, paradoxical insulin secretion at high doses, skin rashes (uncommon)
Octreotide (+/– glucagon)	s.c./i.v. continuous infusion, 6- to 8-hourly s.c. injections	5–25 μg/kg/day	Multiple actions in the β-cell: Inhibits insulin secretion by activation of somatostatin receptor-5 Inhibits calcium mobilization and acetylcholine activity ?Action on the K_{ATP} channel	Gastrointestinal: anorexia, nausea, abdominal pain, bloating, flatulence, loose stools, and diarrhoea, cholelithiasis Endocrine: suppression of GH, TSH, ACTH, glucagon Growth suppression (uncommon) Common problem: tachyphylaxis

Hussain, *Horm Res:* 2008 p2

Take home messages

- Neonatal hypoglycaemia
  - occurs due to an imbalance between glucose supply and utilisation
  - should be suspected and monitored for in high-risk infants
  - cannot be defined by a single BG cut-off and must be tailored to the clinical situation. However most would agree BG <2.6 mmol/L as defining hypoglycaemia
  - should be confirmed by formal blood glucose level and paired critical samples (5.5ml blood, 10-20 ml urine) for insulin, GH, cortisol, FFA, ketones and urine metabolic profile

Take home messages

- Management of neonatal hypoglycaemia
  - ensure adequate glucose intake
    - enteral feeds
    - IV dextrose (10% dextrose through peripheral line)
  - if severe and symptomatic
    - bolus 10% dextrose 2-5ml/kg
    - rapid and excessive dextrose boluses can cause rebound hypoglycaemia in hyperinsulinism
  - constant glucose infusion of 6-8mg/kg/min can work just as well as bolus

Take home messages

  - Refractory cases consider
    - glucagon infusion
      - will work if there are hepatic glycogen stores
    - diazoxide will increase BG even if not hyperinsulinaemic
      - S/E fluid overload, feed intolerance, hypertrichosis long term
    - hydrocortisone can be used briefly
      - check cortisol level prior to aid with diagnosis of adrenal insufficiency/ hypopituitarism
  - Once diagnosis and treatment established, infant should have a trial fast in hospital before discharge

Discussion...