

Neonatal hyperinsulinism

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Definition

- When the glucose is low, and the insulin isn't!

Diagnostic biochemical features

- Glucose infusion rate $>8\text{mg/kg/min}$
- Lab glucose $<3\text{mmol/l}$
 - Detectable insulin/ C-peptide
 - Suppressed/low ketone bodies
 - Suppressed/low serum fatty acids

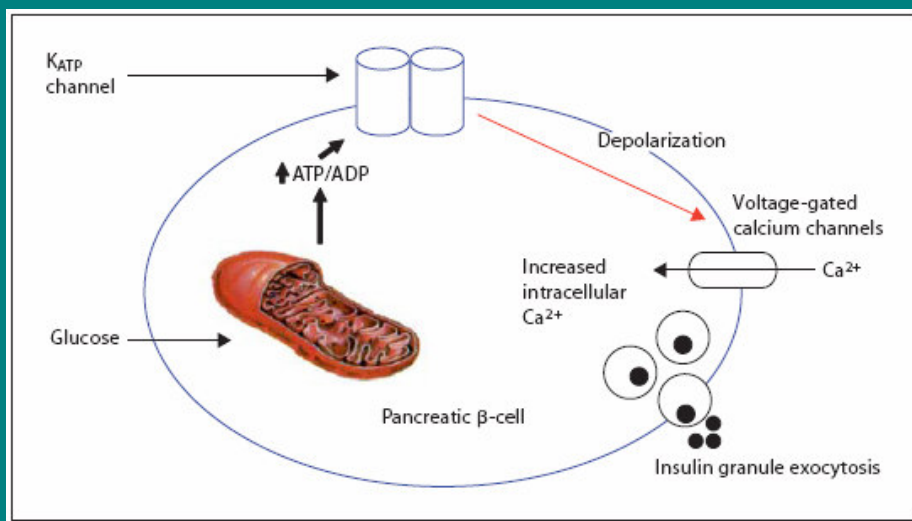
Other tests...

- Indicators of kind of HI
 - Raised serum ammonia
 - Raised serum hydroxybutylcarnitine and urinary 3-hydroxyglutarate
- Supportive evidence (if in doubt)
 - Glucose increases by $>1.5\text{mmol/l}$ with glucagon
 - Glucose increases with octreotide
 - Low serum IGFBP1
 - Provocation testing (in older children)

Clinical features / which babies

- Hypoglycaemia
- Seizures
- Infants of diabetic mothers, small for gestational age, asphyxia, rhesus disease
- Unexpectedly large babies (not always)

Insulin secretion



Hussain K: Diagnosis and Management of Hyperinsulinaemic Hypoglycaemia of Infancy
Horm Res 2008;69:2-13

Other insulin effects

- Lipolysis and ketogenesis are suppressed - no free fatty acids and no ketones
- Glycogenolysis is suppressed
- Gluconeogenesis is suppressed
- Counter-regulatory hormone response to hypoglycaemia is blunted - not enough cortisol, not enough glucagon

Table 1 Serum insulin, total ketone bodies and lactate measurements in seven patients with different forms of HH and at different blood glucose concentrations

| Patient | Cause of HH | Gestation (weeks) | Age at testing (days) | Blood glucose (mmol/l) | Serum insulin (mU/l) | Total ketone bodies (mmol/l) | Plasma lactate (mmol/l) |
|---------|--------------------|-------------------|-----------------------|------------------------|----------------------|------------------------------|-------------------------|
| 1 | Congenital (ABCC8) | 39 | 14 | 2.1/3.9/5.3 | 4.2/12.4/15.4 | <0.05/0.05/0.05 | 1.1/1.2/1.2 |
| 2 | Congenital (ABCC8) | 40 | 12 | 2.6/3.8/5.1 | 13.2/5.6/9.3 | <0.05/0.05/0.05 | 1.3/1.0/1.1 |
| 3 | IUGR (2.3 kg) | 39 | 9 | 2.4/3.5/5.2 | 7.3/12.4/11.6 | <0.05/0.05/0.05 | 1.2/1.3/1.1 |
| 4 | IUGR (2.1 kg) | 38 | 10 | 2.3/3.6/5.6 | 7.5/8.4/8.7 | <0.05/0.05/0.05 | 1.3/1.0/1.1 |
| 5 | Maternal DM | 38 | 2 | 2.0/3.5/5.5 | 6.3/9.5/11.4 | <0.05/0.05/0.05 | 1.4/1.1/1.0 |
| 6 | Maternal DM | 39 | 2 | 1.9/3.7/5.8 | 7.8/9.4/9.7 | <0.05/0.05/0.05 | 1.3/1.5/1.2 |
| 7 | BWS | 38 | 6 | 2.1/4.0/5.5 | 23.4/10.4/8.3 | <0.05/0.05/0.05 | 1.2/1.4/1.2 |

BWS, Beckwith-Weidemann syndrome; Congenital (ABCC8), congenital hyperinsulinism due to mutations in the ABCC8 gene; DM, diabetes mellitus (insulin dependent); HH, hyperinsulinaemic hypoglycaemia; IUGR, intrauterine growth retardation. Total ketone bodies were undetectable in all patients (<0.05 mmol/l). Ketone bodies and lactate were measured at three different blood glucose concentrations (<3 mmol/l, 3–5 mmol/l and >5 mmol/l). Serum ketone bodies were undetectable in all patients at all blood glucose concentrations. The serum lactate remained within the normal range of 1–2 mmol/l.

Hussain K, Blankenstein O, De Lonlay P, Christesen HT: Hyperinsulinaemic Hypoglycaemia: Biochemical basis and the importance of maintaining normoglycaemia during management. *Arch. Dis. Child.* 2007;92;568-570

Hypoglycaemic brain injury

- Widespread neuronal injury
- Grey and white matter changes
- Microcephaly
- MRI abnormalities

- More symptoms, worse handicaps
- Severe, protracted or recurrent hypoglycaemia confers greatest risk

Vannucci RC, Vannucci SJ: Hypoglycaemic brain injury. Semin Neonatol 2001; 6: 147–155

Neurological outcomes

1975-2002, evaluated at mean 14, median 11y

| Neurological outcome by age of onset | | | | |
|--------------------------------------|----------------|---------------|---------------|------------|
| | Neonates 74 | Infants 32 | Children 8 | All 114 |
| All Delay | 34% | 63% | 50% | 44% |
| Mild | 20% | 40% | 25% | 26% |
| Severe | 14% | 23% | 25% | 18% |
| Epilepsy | 22% | 27% | 50% | 25% |

Meissner T et al: CLINICAL STUDY Long-term follow-up of 114 patients with congenital hyperinsulinism. Eur J Endocrinol 2003; 149:43-51

Neurological outcomes

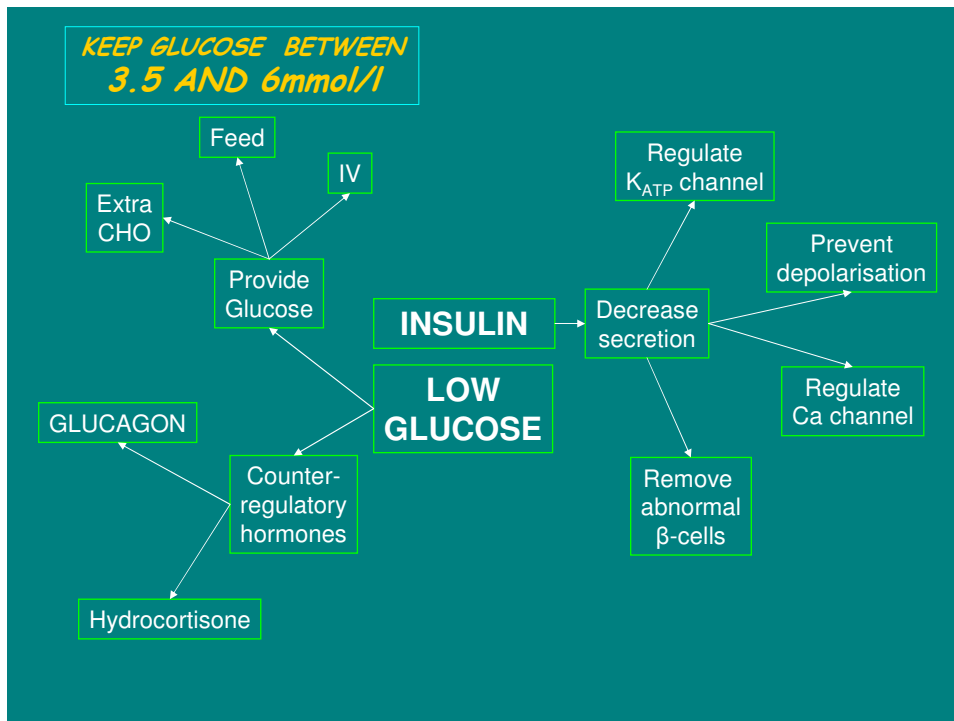
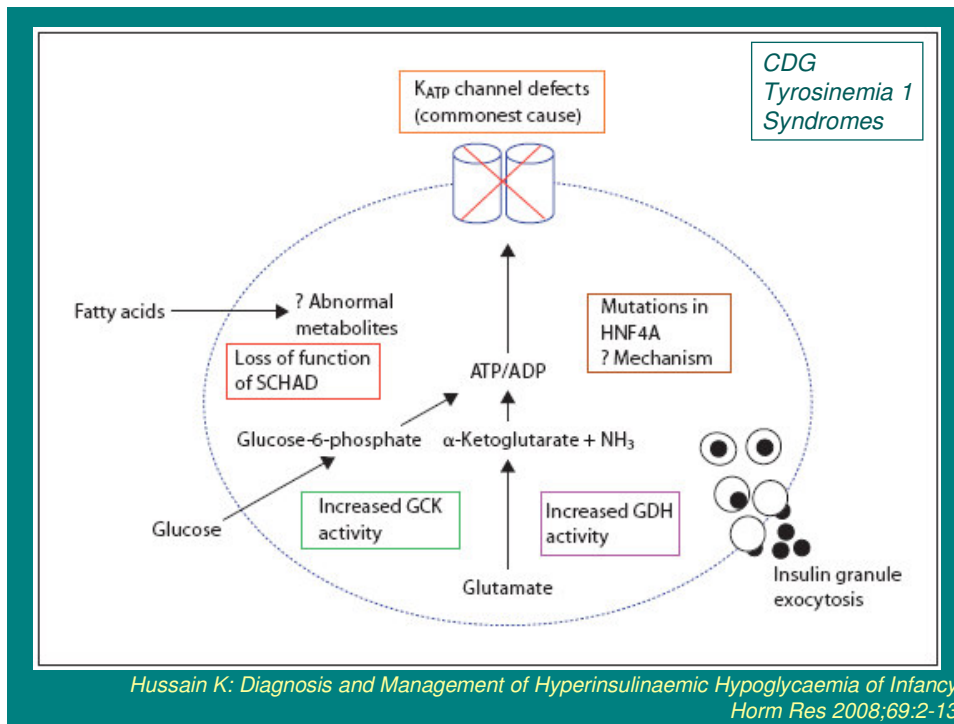
90 patients, 54 neonates, 1982-1998
Dx/Sx, 3, 6, 10 years

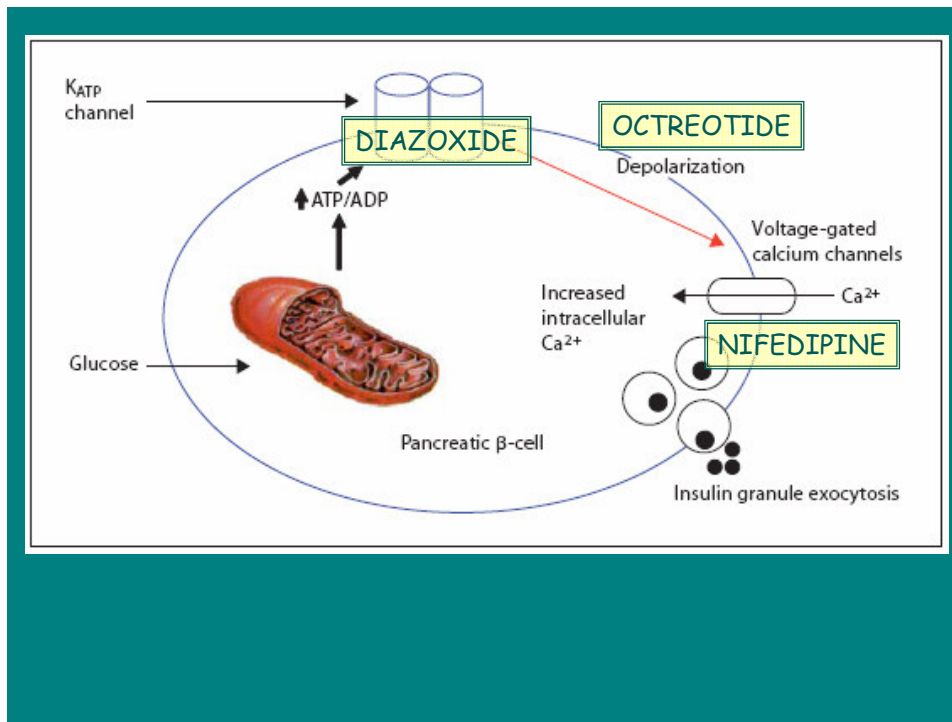
| Neurological outcome by age of onset | | | |
|--------------------------------------|-------------|------------|--------|
| | Neonates 54 | Infants 36 | All 90 |
| Normal | 68% | 82% | 74% |
| All Delay | 32% | 18% | 26% |
| Mild | 21% | 15% | 18% |
| Severe | 11% | 3% | 8% |

*Menni F, de Lonlay P, Sevin C, et al.
Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia.
Pediatrics 2001;107(3):476-9.*

Abnormalities of insulin secretion

- Transient
 - Infants of diabetic mothers
 - Small for gestational age
 - Birth asphyxia
 - Rhesus disease
- Persistent
 - Congenital
 - K_{ATP} channel abnormalities
 - 'Metabolism'





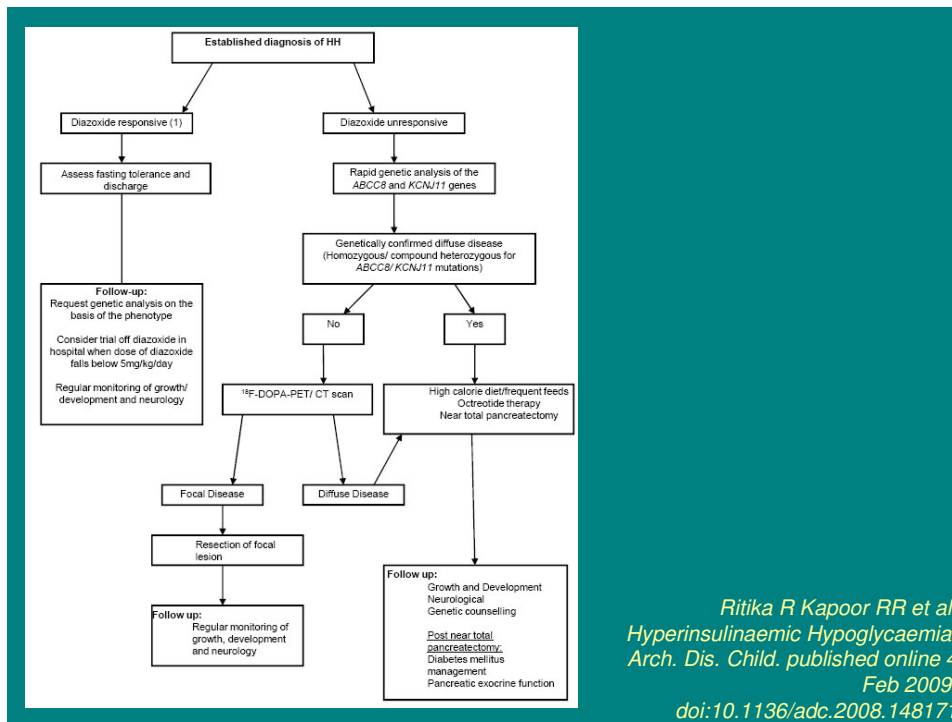
Before surgery

- Focal vs diffuse disease
 - 40-50% focal, 50-60% diffuse
 - Genetics
 - ¹⁸F-L-dopa PET scan
 - 88 or 96% accurate in diagnosing focal vs diffuse
 - Diagnosed 75% of focal lesions
 - 100% positive predictive value for focal, 81% negative predictive value
 - 100% accurate in localising a focal lesion

Hardy OT et al: *Diagnosis and Localization of Focal Congenital Hyperinsulinism by ¹⁸F-Fluorodopa PET Scan.* J Pediatr 2007;150:140-5.

Sperling M: *PET Scanning for Infants with HHI: A Small Step for Affected Infants, A Giant Leap for the Field.* J Pediatr 2007;150:122-24

Hardy OT et al: *Accuracy of [¹⁸F]-fluorodopa PET for diagnosing and localizing focal congenital Hyperinsulinism.* J Clin Endocrinol Metab 2007 Sep 25; Epub ahead of print



Wrapping up

- Hyperinsulinaemia hypoglycaemia in neonates is a life- and brain-threatening illness
- Prompt diagnosis and urgent management is essential
- The mechanisms of hyperinsulinism are being worked out; with hope of therapeutic benefit
- Differentiating focal from diffuse disease has become possible without invasive techniques

Thank You

