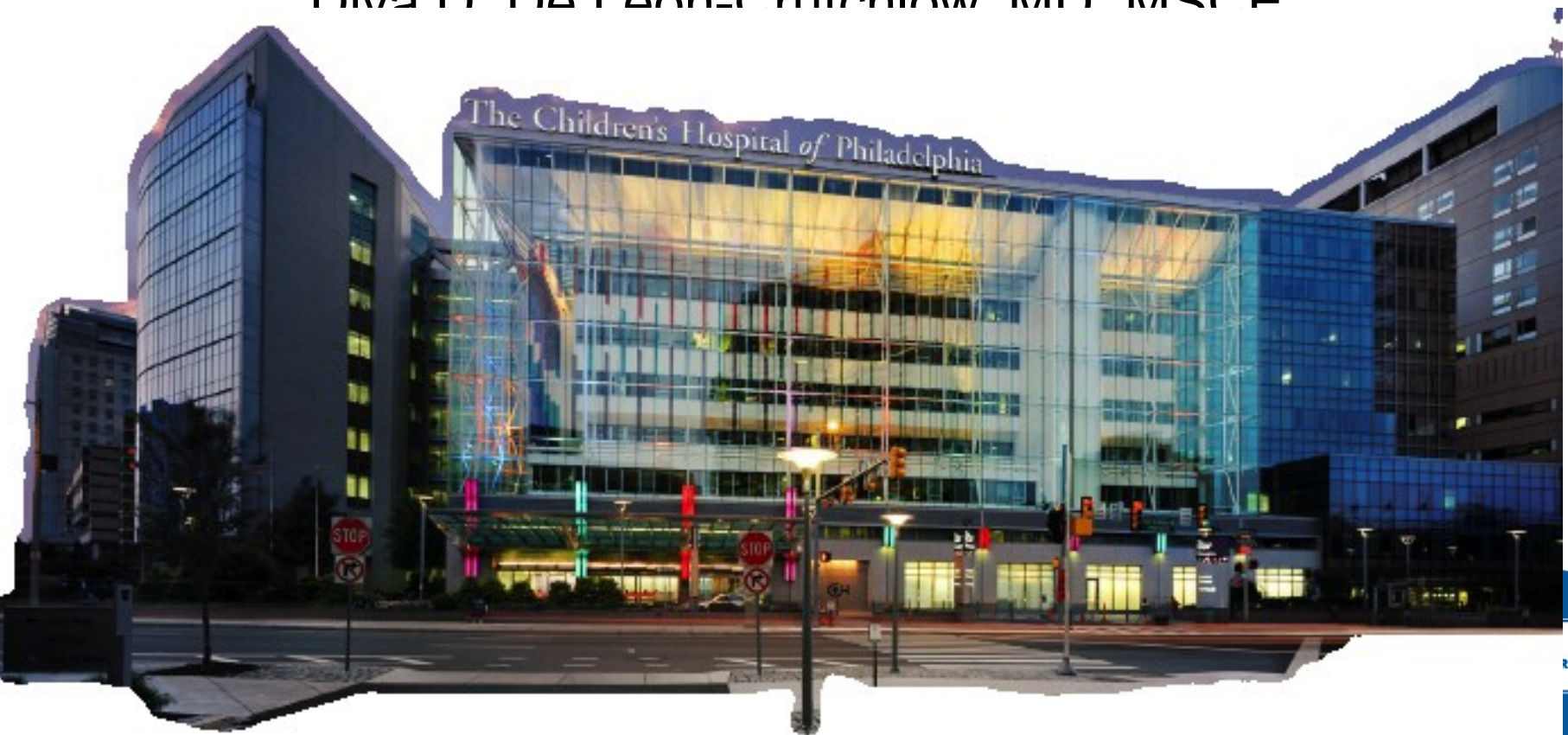




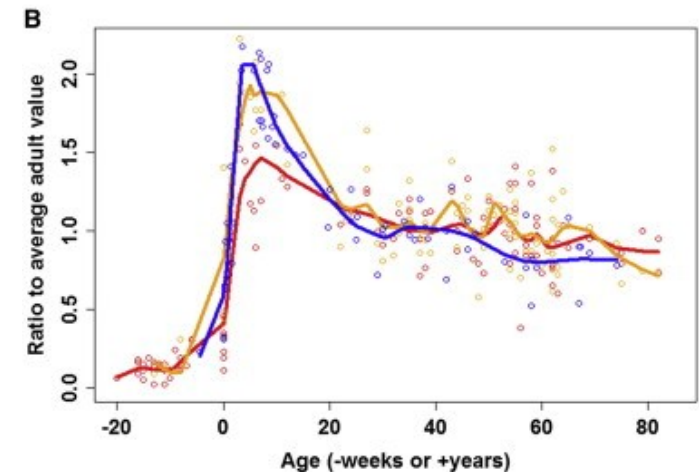
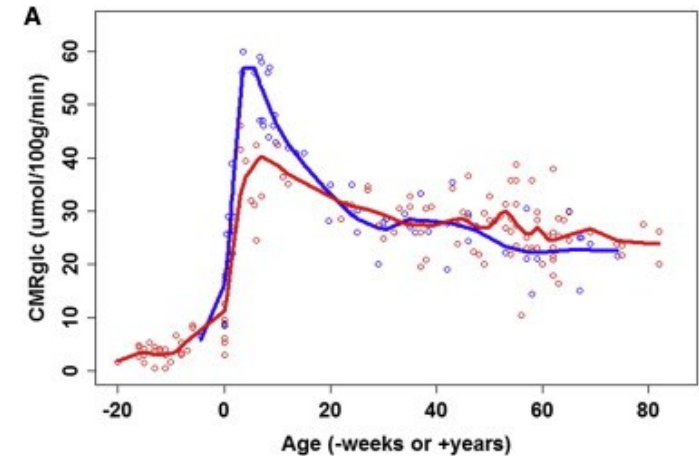
# Developmental and Medical Outcomes

Diva D. De León-Crutchlow MD MSCE



# Effects of hypoglycemia on the developing brain

- Goal of therapy is to prevent brain damage by maintaining normal glucose concentrations
- The developing brain is particularly susceptible to deleterious effects of hypoglycemia
  - Building a human brain is more expensive than maintaining it: infant's brain consumes > 40% of the body's basal metabolic rate (20% in adults) Durnin, 1981
  - White matter volume increases gradually but grey matter volume increases more before age 10--→ glucose consumption is higher in childhood
  - Studies in children with type 1DM have shown effects of frequent hypoglycemic episodes on memory function, verbal IQ and changes on brain volume Northam EA, Diabetes Care 2009
- Children with hyperinsulinism are at high risk for brain damage due to hypoglycemia because they are unable to produce high levels of alternative metabolic brain fuels such as ketones



# Neurodevelopmental Outcomes for Children with Hyperinsulinism

- Factors to consider:
  - Age at diagnosis
  - Delays in making the diagnosis
  - Severity of the hypoglycemia
  - Frequency and duration of episodes of hypoglycemia
  - Type of hyperinsulinism
  - Co-morbidities – seizures
- There is no good longitudinal data
  - Importance of creating a registry
- No uniformity and consistency on neurodevelopmental evaluations
- Highly variable reports 14-44% rates of developmental delays

# Outcomes for Children with Hyperinsulinism treated medically

## ➤ Experience from Israel Mazor-Aranovitch, Eur J Endocrinol, 2007

- 21 Ashkenazi children
  - 11 diffuse and 9 presumed focal (5 had seizures at presentation)
  - Mean age at enrollment 13.7 yrs
- Treatment:
  - Octreotide 10-15 ug/kg/day → 3-4 ug/kg/day (age 6-12 months) + frequent feedings
  - Clinical remission (fasting overnight with BG > 60 mg/dL): age 5 yrs (1.5-12) for diffuse and 1.7 yrs (0.3-5) for focal
- Assessment by telephone interviews with parents (not testing done)
- Outcomes:
  - Early childhood: 4 hypotonia, 8 fine motor problems, 7 gross motor problems, 1 CP, 3 speech problems
  - At school age: all enrolled in regular education, 6 learning problems. None had overt diabetes

# Outcomes for Children with Hyperinsulinism according to type

## ➤ Experience from Paris 1982-1998 Menni, Pediatrics, 2001

- 90 children
  - 63 surgical HI
  - 27 medical HI
- Formal testing performed
- Outcomes:
  - 7 severe psychomotor retardation (6 presented in neonatal period)
  - 12 intermediate disability in 12 patients
  - 16 epilepsy
  - Neonatal onset main risk factor for severe delays
  - Medically treated less severely affected

**TABLE 1.** Percentage of 90 Neonates and Infants With Hyperinsulinism With Subsequent Normal Development (Group 1), Intermediate Disability (Group 2), and Severe Psychomotor Retardation (Group 3)

	<i>n</i>	Group 1	Group 2	Group 3
All patients	90	74%	18%	8%
Neonates	54	68%	21%	11%
Infants	36	82%	15%	3%
Diffuse form	34	75%	14%	9%
Focal form	29	68%	22%	10%
Medical treatment	27	80%	16%	4%



# Outcomes for Children with Hyperinsulinism according to type

## ➤ Experience from Germany 1982-1998 Menni, Pediatrics, 2001

- 114 children
  - 63 surgical HI
  - 47 medical HI (diazoxide) 4 (other)
- Formal testing performed
- Outcomes:

**Table 5** Management and outcome in patients with respect to onset of symptoms.

	Neonatal ( <i>n</i> = 74)	Infantile ( <i>n</i> = 32)	Childhood ( <i>n</i> = 8)	Total ( <i>n</i> = 114)
Operative treatment	70%	25%	38%	55%
Non-surgical treatment	30%	75%	62%	45%
Neuro-developmental retardation	34%	63%	50%	44%
Mild	20%	40%	25%	26%
Severe	14%	23%	25%	18%
Epilepsy	22%	27%	50%	25%

# Outcomes for Children with Hyperinsulinism according to type

## ➤ Experience from CHOP 1980-2000 Steinkrauss, J Ped Nurs, 2005

- 68 children (median age 5.4 yrs)
  - 35 surgical HI
  - 26 medical HI
  - 7 transient HI
- Hypoglycemia questionnaire and standardized developmental assessment tool
- Outcomes:

**Table 3. Developmental Outcomes in 68 Children With HI**

	SIB-R Standard Score Classification			Hypoglycemia Questionnaire
	Average and Above Average (%)	Low and Low Average (%)	Very Low (%)	Special Education/Disability
Overall	69	15	16	12/35
Group A (surgical HI)	68	9	23*	9/22
Group B (medical HI)	73	23	4	3/12
Group C (transient HI)	57	14	29	0/1

\*Versus Group B,  $p < .05$ .

# Long-term Outcomes

- **Gradual improvement in the severity of the hypoglycemia over time**
  - Children treated with intensive medical treatment able to discontinue tube feedings at median age of 10 years
  - Children with diazoxide-responsive hyperinsulinism able to discontinue therapy by their teenager years
  - May still experience hypoglycemia as adults
- **Why does it improve?:**
  - $\beta$ -cell death increased in hyperinsulinism? – *mouse and human data*
  - Increased insulin resistance?



# Long-term Outcomes

- **Improvement of developmental outcomes:**
  - Creating awareness and advocating for screening of neonates at risk: PES hypoglycemia guidelines
  - Better treatment options
  - Early assessment and intervention