UPDATE on NEONATAL HYPOGLYCEMIA

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BACKGROUND

1) NEONATAL HYPOGLYCEMIA IS THE MOST COMMON METABOLIC PROBLEM IN NEONATES

2) THERE IS NO UNIVERSALLY ACCEPTED THRESHOLD FOR SAFE BLOOD GLUCOSE CONCENTRATION DUE TO UNCERTAINTY REGARDING EFFECTS ON NEURODEVELOPMENT
Normal Levels of Glucose

CONTROVERSY IN USA BETWEEN AAP VS THE PES
Postnatal Glucose Homeostasis

Critical in AAP approach

Figure 1: Profile of blood glucose concentrations in the immediate postnatal period

Insulin
Glucagon
Mobilize glycogen
Transitional Neonatal Hypoglycemia: Fetal Glucose “Set Point” Normally Persists For Up To 48 Hours And Then Transitions To An Adult Set Point

THE PES USES MEAN VALUES

AAP USES RANGES FOR OPERATIONAL THRESHOLDS and CLINICAL CONDITION

Marconi, 1996
Srinivasan, 1986
Transitional Hypoglycemia Is Hyperinsulinemia

- Mean plasma glucose for suppression of insulin secretion is 55-65 first 48 hours of life.

- Mean plasma glucose level for suppression of insulin in older infants is 80-85.
  (Glucose sensor-insulin secretion changes after 48 hours of life)

- This Transitional GLUCOSE THRESHOLD for suppression of insulin is at the same level as the adult neuroendocrine response to prevent brain injury 1) insulin suppression 2) glucagon and epinephrine surge. “Neurogenic Response”

- Therefore this Defines “normal” level for the first 48 hours of life (PES)……..55 to 65 mg/dl. Their recommendation is for glucose > 50mg/dl first 48 hours.
Neonatal Regulation of Plasma Glucose Levels
“Beneficial Effects of Biochemical Hypoglycemia”

• The fall in plasma glucose concentrations postnatally is believed to be essential for survival. Includes increased glucose production by glycogenolysis and gluconeogenesis.

• Also stimulation of appetite, adaptation to fast-feed cycles and stimulation of fat metabolism.

• Breast fed infants have lower plasma glucose concentrations than formula fed infants, *but ketone levels are increased in response to breast feeding.*

• Normal physiologic response that all mammals have the first days of life
Normal Glucose levels in “Healthy Term Newborns  Population Meta-Analyses  n=723

AAP Guideline First 24 hours only

<table>
<thead>
<tr>
<th>Time</th>
<th>1-2 hours</th>
<th>3-23 hours</th>
<th>24-47 hours</th>
<th>48-72 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>56</td>
<td>63</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>Estimate of 5\textsuperscript{th} percentile</td>
<td>27</td>
<td>40</td>
<td>41</td>
<td>48</td>
</tr>
</tbody>
</table>

10% fasted prior to screen, only 1/3 breast fed
Wide standard deviation
Probable over estimation of levels

Plasma Glucose Concentrations in Term, AGA, Breast-fed Infants at Four Different Ages (mg/dl)

<table>
<thead>
<tr>
<th>Age (hours)</th>
<th>Mean mg/dl</th>
<th>Median mg/dl</th>
<th>Range mg/dl</th>
<th>Interquartile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>54</td>
<td>50</td>
<td>25-149</td>
<td>41.4-59.4</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>50</td>
<td>28-97.</td>
<td>43.2-59.4</td>
</tr>
<tr>
<td>24</td>
<td>52</td>
<td>52</td>
<td>18-136</td>
<td>46.8-59.4</td>
</tr>
<tr>
<td>72</td>
<td>54</td>
<td>50</td>
<td>25-166</td>
<td>46.8-59.4</td>
</tr>
</tbody>
</table>

Wight et al Breastfeeding Medicine 2006
Continuous Interstitial Glucose Monitoring
(glucose every 5 mins)

Provided Courtesy of Jane Harding
Low glucose concentrations are also common in normal newborns.

Physiologic importance of undetected low CGM is unknown.
Incidence of Neonatal Hypoglycemia in Babies Identified as at Risk In The First 48 Hours Of Life < (“47”)

- At risk groups - SGA, IDM, LGA, Late Preterm (<2500, >4500g)
- Plasma glucose measured before feeds q 3-8 first 48 hours (d/c levels after 3 consecutive normals)
- Dextrose gel and placebo gel (gel x 2 still <47, admit to NICU)
  Also expressed milk prior to delivery for IDM
- These at risk groups represent over 25% of all newborns
- At least 12.5% of all newborns have a low glucose concentration
  - >550,000/year in the United States

Harris, 2012
FINDING the CRITICAL LEVEL for GLUCOSE and NEURODEVELOPMENTAL OUTCOME
EVOLUTION of the DEFINITION of NH as 47

NEURODEVELOPMENTAL APPROACH

- BW <1850 g
- N= 661 infants, 6808 samples,
- Mean (SD) BW 1337 (315) g
- Mean (SD) gestation 30.5 (2.7) wks
- Large Nutrition Study (5 centers)

Sampling
- Daily for all requiring intensive care until clinically stable (2nd to 3rd week)
- Weekly till discharge or weighed 2000g (9th week)
- Developmental Testing

Maximum slope and significance were seen for PDI and MDI when a cut off of 45mg/dl was used.

2/3 had <47mg/dl ranging from 3 to 30 days. Median age onset was 2 days.

Reduced development scores were associated independently with number of days on which level was < 47mg/dl.

(A number of infants had glucose < 20 for 5 days)

Not sustained at 7-8 years of age!!!!!!!
Later author says method not optimal

<table>
<thead>
<tr>
<th>Days of NH</th>
<th>Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3 - 4</td>
<td>2.2 : 1</td>
</tr>
<tr>
<td>≥ 5</td>
<td>3.5 : 1</td>
</tr>
</tbody>
</table>
Aim and Design:

- To compare the neurodevelopmental outcome of preterm (<32 weeks) who had frequent low blood glucose levels (<47mg/dl ) in the first ten days of life vs that of matched controls.
- Prospective, Observational
- Daily glucose as well as other samples recorded the first 10 days
- Index 3 days <47, controls all > 47 (47/566)
MEAN GRIFFITHS DEVELOPMENTAL QUOTIENTS OF 47 MATCHED PAIRS (2 Years)

Tin W. Early Human Develop 2005
### Summary of Assessments at 15-16 years

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>Index</th>
<th>Mean paired difference</th>
<th>Number of pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Scale IQ (Short Wechsler-III)</td>
<td>80.7±19.8</td>
<td>81.2±15.16</td>
<td>-0.6 (-8.3 to +7.2)</td>
<td>38</td>
</tr>
<tr>
<td>Reading (Wechsler WORD score)</td>
<td>91.1±18.3</td>
<td>90.2±15.18</td>
<td>+0.9 (-7.5 to +9.2)</td>
<td>36</td>
</tr>
<tr>
<td>Behaviour (Total Aschenbach score)</td>
<td>51.0±10.2</td>
<td>54.4±13.8</td>
<td>-3.4 (-9.3 to +2.5)</td>
<td>37</td>
</tr>
<tr>
<td>Adaptation to Daily Living (Vineland)</td>
<td>74.4±19.1</td>
<td>68.5±16.7</td>
<td>+5.9 (-2.8 to +14.7)</td>
<td>37</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>6</td>
<td>4</td>
<td>-</td>
<td>47</td>
</tr>
</tbody>
</table>

Win Tin et al Pediatrics 2012
Quadrigenta Septum Phobia profoundly influenced neonatal care

Do you really know how many times my blood glucose went below 47mg/dl? YES! ALOT

(courtesy Win Tin)
Hypothesis: The neuropsychological development of 2 and 4.5 year old children is related to the severity, duration, and frequency of low glucose concentrations in the neonatal period (n=614 @ Risk)
Key Findings From CHYLD@2y

In at risk babies screened and treated with the aim of keeping blood glucose concentrations >47 mg/dl:

1. There were long and undetected periods of interstitial glucose concentrations ≤ 47mg/dl
2. High or unstable glucose concentrations were associated with worse developmental outcomes. “U shaped curves” morbidity @ low and high levels

McKinlay et al, NEJM 373: 2507, 2015
Undetected Low Glucose Concentrations

In at risk babies screened and treated with the aim of keeping blood glucose concentrations > 47 mg/dl:

• 53% experienced blood glucose < 47mg/dl
• 23% had glucose concentrations <47mg/dl not detected on intermittent blood testing.
• 25% of those treated had glucose concentrations < 47mg/dl for >5 hours in the first week

McKinlay et al, NEJM 373: 2507, 2015

CHYLD
Children with Hypoglycaemia and their Later Development
# Undetected Hypoglycemia and Outcome at 2 Years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No events (N=108)</th>
<th>≥1 Interstitial episode (N=33)</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosensory impairment</td>
<td>42%</td>
<td>42%</td>
<td>1.01 (0.66, 1.54)</td>
</tr>
<tr>
<td>Processing difficulty</td>
<td>17%</td>
<td>17%</td>
<td>0.92 (0.38, 2.23)</td>
</tr>
</tbody>
</table>
Association of Neonatal Glycemia with Neurodevelopment at 4.5 y

N=614 >32 weeks with at least one neonatal risk factor for Hypoglycemia (2006-2010)

• Blood Glucose but Masked interstitial measurements up to 7 days

• Hypoglycemia (NH) <47mg/dl whole blood treated to maintain > 47 mg/dl

• NH definitions =@ least one episode< 47, severe = < 36, recurrent = > 3 episodes. Interstitial lasted > 10 minutes <47mg/dl

Mckinlay et al Jama Peds 2017 CHYLD
RESULTS

• 477/604 were assessed (79%)
• 280 (58.7%) exposed to Hypoglycemia did not have increased neurosensory impairment (visual, deafness, CP, IQ>1sd below mean)

• Hypoglycemia was associated with increased risk of low executive function, and lower visual motor function
• Highest risk in those exposed to severe, recurrent, or clinically undetected (interstitial) hypoglycemia

Mckinlay et al Jama Peds 2017 CHYLD
Conclusions and Relevance

- NH was not associated with increase risk of combined neurosensory impairment at 4.5 years

- NH was associated a dose dependent increased risk of poor executive function and visual motor function, even if not detected clinically.

- Will this influence later learning?
EXECUTIVE FUNCTION

• Collective capacity for problem solving, planning, attention control and goal-directed behavior.

• Children have difficulty remembering and carrying out instructions, staying focused, and planning and monitoring progress with a specific task, which can affect not only daily activities but also learning.

• Prefrontal cortex is responsible for proper development of EF and increased activation of this region is associated with better academic functions and EF.

• Development of prefrontal cortex and EF is continuous from childhood through adolescence and into early adulthood

Shah et al, Neonatology in press 2018
Dextrose Gel
Insert 0.5 mls into right buccal cavity

Massage for a few seconds

Repeat this process, alternating sides until entire dose has been administered.
Dextrose Gel for Neonatal Hypoglycemia (Sugar Babies Study) RCT

Randomized double blind placebo controlled trial (New Zealand)

- 35-42 wks, < 48 hours old @ risk 1:1 randomization
- 40% dextrose gel (200mg/k) or placebo gel
- Randomization stratified by maternal diabetes and BW
- Hypoglycemia < 47mg/dl
- Treatment failure < 47 after 2 tx

RESULTS

- 242/547 (47%) were hypoglycemic and then randomized
- Dextrose gel reduced treatment failure vs placebo 14% vs 29%

FINDINGS

- Treatment with dextrose gel is inexpensive and simple to administer. Dextrose gel should be considered for first line treatment to manage hypoglycemia in LPT and Term in first 48 hours after birth.

Harris DL et Al Lancet 2013
Screening and management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants (PEDS March 2011, reaffirm 2016)

[(LPT) Infants 34 – 36 6/7 weeks and SGA (screen 0-24 hrs); IDM and LGA ≥ 34 weeks (screen 0 -12 hrs)]

<table>
<thead>
<tr>
<th>Symptomatic and &lt;40mg/dl</th>
<th>IV Glucose</th>
</tr>
</thead>
</table>

**ASYMPTOMATIC**

<table>
<thead>
<tr>
<th>Birth to 4 hours of age</th>
<th>4 – 24 hours of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>INITIAL FEED WITHIN 1 Hour</td>
<td>Continue feeds q2-3 hours</td>
</tr>
<tr>
<td>Screen glucose 30 minutes after 1st feed</td>
<td>Screen Glucose prior to each feed</td>
</tr>
<tr>
<td>Initial Screen &lt;25mg/dl</td>
<td>Screen &lt;35mg/dl</td>
</tr>
<tr>
<td>Feed and check in 1 hour</td>
<td>Feed and check in 1 hour</td>
</tr>
<tr>
<td>&lt;25mg/dl</td>
<td>&lt;35mg/dl</td>
</tr>
<tr>
<td>IV Glucose*</td>
<td>IV Glucose*</td>
</tr>
<tr>
<td>25 – 40mg/dl</td>
<td>35 – 45mg/dl</td>
</tr>
<tr>
<td>Refeed/IV Glucose* as needed</td>
<td>Refeed/IV Glucose* as needed</td>
</tr>
</tbody>
</table>

**Target Glucose screen ≥45mg/dl prior to routine feeds**

*Glucose dose = 200mg/kg (dextrose 10% at 2ml/kg) and/or IV infusion at 5 – 8mg/kg/min (80 – 100ml/kg/d)
Achieve plasma glucose 40 – 50mg/dl.

Symptoms of Hypoglycemia include: Irritability, tremors, jitteriness, exaggerated moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding.