GLUCAGON CHALLENGE TEST - RECURRENT HYPOGLYCEMIA

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Guide:
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Measurement of thyroid hormones – hypothyroidism

Measurement of cortisol – Addisons disease

Measurement of C-peptide – type of Diabetes

Measurement of LH, FSH and estradiol, testosterone – Pubertal disorders

Measurement of GH levels – GHD

Can measurement of insulin levels ALONE at time of hypoglycemia – make a diagnosis of hyperinsulinemia?
Problems with insulin assay

Insulin concentration measured in peripheral plasma may be up to 90% lower than the initial peak plasma concentration within 30 minutes (intra and extra vascular distribution, clearance by liver on passage).

Hemolysis (difficult sample drawing) – enzyme release from RBC – destroys insulin.

Store in 4 deg celsius, maximum for one day.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cut - off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson</td>
<td>2 µU/mL</td>
</tr>
<tr>
<td>Sperling text book of pediatric endocrinology</td>
<td>5 µU/mL</td>
</tr>
<tr>
<td>Brook text book of pediatric endocrinology</td>
<td>EVEN DETECTABLE INSULIN AT THE TIME OF HYPOGLYCEMIA IS HYPERINSULINEMIA</td>
</tr>
</tbody>
</table>
What is the alternative then?

- IGFBP-1 – not available in India
- Ketone testing – practically useful but some pitfalls
  Poor fat stores – cannot mount ketotic response

*Ketonuria does not exclude hyperinsulinemic hypoglycemia.*
*Wolfsdorf JI, Sadeghi-Nejad A, Senior B.*
CASE 1

Master H one and half year old male child

Presented with seizures on d4 of life : CBG :33mg/dL

Then on re-examination, hypoglycemic seizures noted in 5th month, 6th month, 7th month and 1 year of age...

No family history of hypoglycemia or early diabetes

On examination – No clinical markers

Anthropometry – normal growth

Height SD score -1.5, target height SD score -1.3
Supervised fast test done:

<table>
<thead>
<tr>
<th>CRITICAL SAMPLES</th>
<th>Value</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Blood Glucose</td>
<td>46mg/dL</td>
<td>Low</td>
</tr>
<tr>
<td>Blood Ketones</td>
<td>NEGATIVE</td>
<td>Non Ketotic</td>
</tr>
<tr>
<td>Serum GH</td>
<td>1.2 ng/mL</td>
<td>Low</td>
</tr>
<tr>
<td>Serum Cortisol</td>
<td>25.3 µg/dL</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum Insulin</td>
<td>7.8 µU/mL</td>
<td>Elevated</td>
</tr>
<tr>
<td>Serum Ammonia</td>
<td>86 µg/dL</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Is it hyperinsulinemia or GH deficiency?
Glucagon challenge test done

- Basal Blood sugar - 46 mg/dL
- Inj glucagon 30µg/kg given IV - No Dextrose bolus given
- Repeat Blood sugar at 30 minutes - 84 mg/dL

This is hyperinsulinemia - child started on diazoxide after taking blood for genetic studies
### Home monitoring of blood glucose

<table>
<thead>
<tr>
<th>Prior to Diazoxide therapy (morning)</th>
<th>After Diazoxide (10 mg/kg) Morning</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>76</td>
</tr>
<tr>
<td>65</td>
<td>84</td>
</tr>
<tr>
<td>45</td>
<td>89</td>
</tr>
<tr>
<td>73</td>
<td>82</td>
</tr>
<tr>
<td>56</td>
<td>90</td>
</tr>
<tr>
<td>32</td>
<td>79</td>
</tr>
<tr>
<td>65</td>
<td>100</td>
</tr>
<tr>
<td>54</td>
<td>95</td>
</tr>
<tr>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>
CASE 2

Master B – 2 year old developmentally normal male child

Presented with low sugar in D2 of life

Recurrent hypoglycemias since then

Varied work up. Previous critical sample taken – ketones negative, insulin 31 µIU/mL

On examination: Short

a) Height SD score -2.5

b) Target height SD score -1.3

c) Weight SD score -1.1

Pathologic short stature
### CASE 2

<table>
<thead>
<tr>
<th>CRITICAL SAMPLES</th>
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<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Blood Glucose</td>
<td>43 mg/dL</td>
<td>Low</td>
</tr>
<tr>
<td>Blood Ketones</td>
<td>Negative</td>
<td>Non-ketotic</td>
</tr>
<tr>
<td>Growth Hormone</td>
<td>1.4 ng/mL</td>
<td>Low</td>
</tr>
<tr>
<td>Serum Cortisol</td>
<td>27.7 µg/dL</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum Insulin</td>
<td>0.2 µU/mL</td>
<td>Below the cut-off, but detectable</td>
</tr>
</tbody>
</table>

Previous FAO screen work-up twice – Negative

Is it GH deficiency or Hyperinsulinemia?
Glucagon challenge test done

- Basal Blood sugar – 42 mg/dL
- Inj glucagon 30µg/kg given IV – No Dextrose bolus given
- Repeat Blood sugar at 30 minutes – 40 mg/dL

This is NOT hyperinsulinemia – GH deficiency more likely
A diagnosis of GH deficiency was arrived at – child has been started on GH – no hypoglycemic episodes since then.
Master S was a 3 months baby.
He had documented three episodes of hypoglycaemia.
Delivered as a preterm baby – Non consanguineous parents.
Child had failure to thrive with height SD score of -4.5, weight SD score of -5.6.
Had significant risk factors and classical features of sepsis
Admitted in PICU – required a GIR 12 mg/kg/min to maintain sugars
No clinical markers of endocrine dysfunction.
Developmental milestones are normal.
GCT : rise of 50mg/dl
**CASE 3**

Critical sample taken in view of persistent hypoglycemia

EM work-up negative, FAO work-up negative, lactate and pyruvate normal

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<tr>
<th>CRITICAL SAMPLES</th>
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<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOOD GLUCOSE</td>
<td>38 mg/dL</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>BLOOD KETONES</td>
<td>Negative</td>
<td>Non-ketotic</td>
</tr>
<tr>
<td>GROWTH HORMONE</td>
<td>12.6ng/mL</td>
<td>N growth hormone</td>
</tr>
<tr>
<td>SERUM CORTISOL</td>
<td>12.5 µg/dL</td>
<td>Cortisol replete</td>
</tr>
<tr>
<td>SERUM INSULIN</td>
<td>1.3µU/mL</td>
<td>Detectable, but below the textbook cut-off of 2µU/mL</td>
</tr>
</tbody>
</table>
Glucagon challenge test done

- Basal Blood sugar – 40 mg/dL
- Inj glucagon 30µg/kg given IV – No Dextrose bolus given
- Repeat Blood sugar at 30 minutes – 76 mg/dL

This is hyperinsulinemia – probably transient related to sepsis
Infection was treated and no subsequent hypoglycemia
At 1 year of age, all developmental milestones and normal activity.
<table>
<thead>
<tr>
<th>Case</th>
<th>Screening test</th>
<th>Diagnostic test</th>
<th>Confirmatory evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Master H Permanent PHHI</td>
<td>Elevated insulin (7.8 (\mu U/mL)) Low GH (1.2 ng/mL) Negative ketones</td>
<td>Increment of glucose &gt; 30 mg/dl with glucagon</td>
<td>Response to Diazoxide Genetic tests (awaited)</td>
</tr>
<tr>
<td>Master B GHD</td>
<td>Varied insulin levels (0.2 (\mu U/mL) and 31 (\mu U/mL)) Low GH (1.4 ng/mL)</td>
<td>No Increment of glucose with glucagon</td>
<td>MRI – hypoplastic pituitary Response to GH</td>
</tr>
<tr>
<td>Master S Transient hyperinsulinemia</td>
<td>Marginally elevated insulin (1.3 (\mu U/mL)) Normal GH (12.6 ng/mL)</td>
<td>Increment of glucose &gt; 30 mg/dl with glucagon</td>
<td>Evidence of sepsis After treating sepsis, no hypoglycemia</td>
</tr>
</tbody>
</table>
Maintenance of glucose homeostasis

**INSULIN EFFECTS**
- Glucose uptake
  - Lipolysis
  - Ketogenesis
  - Gluconeogenesis
  - Glycogenolysis

**COUNTER REGULATORY HORMONE EFFECTS**
1. Glucagon
2. Adrenaline
3. Cortisol
4. Growth hormone

**Blood glucose**

**BLOOD GLUCOSE**
**GLUCAGON STIMULATION TEST**

Baseline Venous Blood sugar - Hypoglycemic

30 microgram/kg glucagon injected iv – No dextrose bolus

After an hour venous blood sugar levels checked

**INCREMENT OF GLUCOSE > 30 mg/dl**
- Appropriate conservation of liver glycogen with hypoglycemia
- Indicates suppression of liver glycogenolysis by excessive insulin

**INCREMENT OF GLUCOSE < 30 mg/dl**
- No liver glycogen - depleted
- Not due to excess insulin
P R A C T I C A L A S P E C T S

- Glucagon stimulation test - - Must be done in ER/ PICU (back-up)

- All resuscitative measures must be kept handy

- Glucagon - cost INR 700/-, available easily

- Venous sugars must, don’t restrict to CBG
To summarize

Three cases of ambiguous cause of hypoglycemia - Glucagon challenge - gave the answer

Simple, safe, and cost-effective test

Simple test for an expensive confirmatory investigation (MRI/genetic test) and a very tedious treatment

All E-rooms must be equipped with glucagon and be used judiciously.

THANK YOU