An interesting case of recurrent seizures

By
Dr S. Murugarajan
Final yr DNB pg
Dr Kannan HOD
Railway hospital, Perambur.
A 6 months old male infant, 1st born of second degree consanguineous parents brought at 20 days of life with complaints of recurrent seizures from day 3 of life.
This infant born at term, LSCS delivery to a primi mother, indication being Primi with CPD.

**Birth wt 3.75 kg**. Cried immediately after birth. Direct breast feeds started within 2 hours after birth.

**On day 3** of life, at 5 30 pm baby became lethargic, there was poor feeding and decreased tone for which baby was taken to a private hospital and got admitted and improved after treatment.
On day 5 of life, at 9 30 pm baby had one episode of tonic clonic seizures involving all limbs associated with staring look and increased sweating over body.

At that time baby was found to be hypoglycemic and stabilised.

On day 13 of life morning 3 45 am baby developed abnormal movements involving Right upper limb lasting for 2-3 min. This episode was also associated with hypoglycemia and managed appropriately.
On day 20 of life baby developed uprolling of eyes with twitching of left eyelid associated with shrill cry around 5 episodes lasting for 1-2 min.

History of profuse sweating associated with these episodes.

In view of recurrent seizures baby admitted to railway hospital on day 20 of life for evaluation.
In between seizure episodes baby feeds well, alert, active, interacting well with mother, passing urine, motion normally.
The seizure episodes has no relation to feeding.
- No h/o fever.
- No h/o vomiting, diarrhoea, abdominal distension.
- No h/o cough, cold, fast breathing.
- No h/o polyuria, oliguria, abnormal odour in urine, yellow coloured urine.
- No h/o rash, bleeding.
- No h/o icterus, umbilical discharge.
- No other significant medical history.
Antenatal h/o: mother conceived at 23 yr of age- spontaneous conception.

Booked, immunised, Regular antenatal check up done. Fe & FA taken.

No h/o DM/ HT/ Hypothyroid/epilepsy/ fever with rash/ any other significant illness/ drug intake.
Family H/o: 1st child born to second degree consanguineous marriage.

No neurological illness or other significant medical illness runs in the family.

Child was given exclusively breast feed from day 1 of life.
On examination at 20 days of life...

- Alert, active.
- No pallor, icterus, cyanosis.
- Vitals stable.
- Wt - 4 kg
- Length - 50cm
- OFC - 37cm
- Head appears **normal**, ant fontanelle – open (2.5*2.5cm), posterior fontanelle – closed, sutures normal.
- Face- appears normal
- Eyes including fundus – normal
- Ears, nose – normal.
- Oral cavity- **natal teeth** 2 lower central incisor present.
- Extremities- **b/l post axial polydactyly** present in upper limbs and lower limbs.
- External genitalia – normal.
- Spine and back- **solitary capillary hemangioma** of size 0.5*0.5 cm over mid thoracic spine present.
Systemic examination

- CNS – Normal
- CVS - normal
- RS - normal
- ABDOMEN - normal
- MUSCULOSKELETAL - normal
- GENITO-URINARY - normal
Baby had seizures with documented hypoglycemia twice in the hospital.

Seizures controlled immediately following iv dextrose bolus.

Baby initially maintained euglycemia with daily maintenance fluids.

Subsequently developed erratic hypoglycemia inspite of iv fluids and breast feed.

No Anti epileptic drug therapy needed to control seizures at any point of time.
20 day old male baby 1ˢᵗ born of second degree consanguineous marriage born to primi mother whose antenatal period uneventful, born at term, LSCS, B wt - 3.75kg, developed recurrent episode of hypoglycemic seizures. On examination natal teeth, midline capillary hemangioma, post-axial polydactyly present.
CBC including smear - normal

Septic screen – CRP, Blood c/s, urine c/s - normal.

LFT, RFT, Electrolytes – normal.

Serum calcium - 11.1 mg/dl (normal).

Serum phosph - normal.

Serum magnesium - normal.

Uric acid - normal.
- Blood glucose $< 40 \text{ mg/dl}$ at the time of seizure.
- Plasma ammonia - 72 micromol/l (11-35)
- ABG – normal
- Plasma lactate - 16mg/dl ($<26$)
# Critical sample analysis

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose - 36mg/dl</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>Lactate - 16mg/dl</td>
<td>normal</td>
</tr>
<tr>
<td>Ammonia - 72micromol/l</td>
<td>Mildly elevated</td>
</tr>
<tr>
<td>Ketones - negative</td>
<td>Non-ketotic</td>
</tr>
<tr>
<td>Cortisol (morning sample) 23.3 microgm/dl</td>
<td>normal</td>
</tr>
<tr>
<td>Growth Hormone - 16.6</td>
<td>normal</td>
</tr>
<tr>
<td>Thyroid profile - normal</td>
<td>normal</td>
</tr>
<tr>
<td>INSULIN - 21.54microIU/ml</td>
<td>HYPERINSULINISM</td>
</tr>
</tbody>
</table>
Karyotyping done: normal
Urine metabolic screen: negative
Imaging: Echo, MRI brain, USG abd- normal.
Final diagnosis

- Congenital hyperinsulinism with hyperammonemia
 Oral Diazoxide 25mg BD given.

 Frequent feeds.

 Home monitoring of hypoglycemia.

 During illness watch for hypoglycemic symptoms and report immediately.

 Health education regarding ds nature and need for continuation of therapy.
Now child maintaining euglycemia on diazoxide.

Developmentally age appropriate milestones attained.

Gaining weight adequately.

Tolerating therapy well.
DISCUSSION
In neonates there is no obvious correlation between blood glucose concentration and classic clinical manifestations of hypoglycemia.

Many authorities recommend Any blood glucose values < 50 mg/dl should be treated aggressively.

Whole blood glucose < 50mg/dl (10-15% higher for serum or plasma values).
Many definitions...

- Epidemiological definition: < 2SD = to 20mg/dl.
- Clinical defn – based on whipples triad.
- Operational threshold not to make diagnosis but for intervention:
  1. any baby < 20-25mg/dl
  2. for term infants: < 24hrs - 30-35mg/dl; >24 hrs - 45-50mg/dl
  3. infants with abnormal symptoms: 45mg/dl.

**Absence of symptoms at low glucose level does not rule out CNS injury.**
Recurrent or sustained hypoglycemia may lead to permanent impairment of brain growth and function.

Major long term sequelae are mental retardation, recurrent seizure activity, subtle changes in personality.

There is no precise knowledge relating duration or severity of hypoglycemia to subsequent neurologic development of children in a predictable manner.
Physiology in newborn...

- There is abrupt transition from Intrauterine life (constant glucose supply) to extrauterine life (intermittent glucose supply).
- To maintain blood glucose concentration an elaborate regulatory system evolved.
- This regulatory system consists of Autonomic nervous system, hormones, changes in receptors, changes in key enzymes.
Major causes of hypoglycemia in a neonate:

Transient hypoglycemia:

- Small for gestational age
- Premature babies
- Hypothermia
- Hypoxia
- Neonates with perinatal asphyxia
- Infants of a diabetic mother
- Infants with erythroblastosis fetalis
- Neonates born to mother with toxemia
Causes of recurrent hypoglycemia

- Hyperinsulinism
- Panhypopituitarism
- Isolated GH deficiency
- ACTH deficiency
- Addison ds
- Epineprine def
- Glycogenesis and gluconeogenesis disorder
- Lipolysis disorder
- FAO disorder
- Aminoacid and organic acid disorder
- Miscellaneous- liver ds, drugs, diarrhoea, sepsis.
Clinical features of hypoglycemia:

- **Autonomic nervous system activation (epinephrine release):** Sweating, tremulousness, palpitations (tachycardia), anxiety, hunger, nausea, vomiting, and weakness.

- **Decreased cerebral glucose level:** Headache, confusion, visual disturbances, lethargy, restlessness, inability to concentrate, somnolence, personality changes, seizures, and even coma.
Symptoms of hypoglycemia in infants:

- more subtle
- cyanosis, apnea, hypothermia, hypotonia, lethargy, jitteriness and seizures.

Hypoglycemia: always be suspected in a case of convulsion, coma, or sudden deterioration in neurobehavioral functioning.
Simultaneous measurement of following substrates in the same sample at the time of clinically manifested hypoglycemia – termed as critical sample.

Substrates analysed are Glucose, FFA, ketones, lactate, uric acid, ammonia.

Hormones measured are Insulin, cortisol, GH, thyroxine, TSH, IGF-BP1.

Samples analysed during hypoglycemia and 30 mins after Glucagon admn. Rise in glu > 40 mg after Glucagon given at the time of hypoglycemia strongly suggests HYPERINSULINEMIC STATE.
Congenital Hyperinsulism / nesidioblastosis

- MCC of persistent hypoglycemia in early infancy.
- Onset from birth to 18 months of age.
- Result of familial or non-familial nesidioblastosis or islet cell dysmaturity syndrome.
- Islet cell adenoma usually present in a child 5 years or older.
Features of hyperinsulinism

- Ravenous appetites, increased demand for food and weight gain.
- Jitteriness and seizures common.
- Macrosomia present
- Nondiabetic mother.

If hyperinsulinism present differentiate: diffuse B cell hyperplasia or focal B cell microadenoma.
(a) Beta cell at rest. The $K_{\text{ATP}}$ channel is open and the cell is at its resting membrane potential.

1. Glucose in blood

2. Metabolism slows

3. ATP

4. $K_{\text{ATP}}$ channel open

5. Cell at resting membrane potential

6. Voltage-gated $Ca^{2+}$ channel closed

7. No insulin secretion

(b) Beta cell secretes insulin. Closure of $K_{\text{ATP}}$ channel depolarizes cell, triggering exocytosis of insulin.

1. Glucose in blood

2. Glycolysis and Citric acid cycle

3. ATP

4. $K_{\text{ATP}}$ channel closed

5. Less $K^+$ leaves cell

6. Cell depolarizes

7. $Ca^{2+}$ channel opens

8. $Ca^{2+}$ entry triggers exocytosis and insulin is secreted

>$5 \text{ mmol}$
- Glucokinase (GK) is the rate limiting step for glucose metabolism by the islets.
- Generation of ATP from the electron transport chain closes an ATP-dependent potassium channel.
- Opens a voltage-dependent calcium channel.
- Increase intracellular calcium leads to the stimulation of insulin secretion.

Diabetes 1996; 45: 223-241
ATP

K
ATP channel

glucose

glycolysis

ATP

K+

K_ATP channel

Inset: 10 mmol/L glucose

(mV)

-10

-60

1 min
ATP voltage-dependent $Ca^{2+}$ channel

$K_{ATP}$ channel

$G_{K}$

glucose

ATP

$K^{+}$

$Ca^{2+}$

voltage-dependent $Ca^{2+}$ channel
Reserve Pool

Readily Releasable Pool

- calcium-dependent kinesin-dependent movement on microtubules
- myosin Va-dependent movement on actin microfilaments

ATP

SNARE proteins

Ca^{2+}
Discovery of **K<sub>ATP</sub> independent** effects of glucose

- By circumventing the ‘triggering’ pathway, it can be shown that glucose also acts to ‘augment’ insulin secretion through separate mechanisms
The ATP-sensitive K+ Channel

- Composed of 4 pore forming subunits and 4 accessory subunits
- Much like glucokinase there are activating and inactivating mutations
- Also the target of diabetes drugs (sulphonylureas) that mimic the effect of glucose by inhibiting the channel
Type 1:
- inherited forms (autosomal recessive/AD)
- sporadic forms
- inactivating mutation in Kir 6.2 or SUR subunits (located in chromosome 11)
- severe hypoglycemia in newborn period, requiring high glucose infusion rate.
- medical therapy not much useful, mostly requires surgery.
Type 2:
- autosomal dominant inheritance
- age of onset symptoms 6 months
- less severe hypoglycemia
- activating mutation in glucokinase.
- medical management works well, surgery needed if fails.
Type 3:
- usually sporadic rarely dominant inheritance.
- hypoglycemia associated with mild and persistent hyperammonemia with concentration around 100-200 micromol/l.
- activating mutation in the enzyme Glutamate dehydrogenase. This enzyme oxidises glutamate and thereby increases insulin and also increases ammonia in liver.
- There is no CNS symptoms due to hyperammonia.
CT / MRI – not necessary routinely as macroadenoma very rare in infancy perod.

18-F-L-dopa PET scan may be useful in differentiating focal from diffuse variety.

Genetic analysis ultimately needed to differentiate focal from diffuse variety and for classification.
Drugs:
1. oral diazoxide 10-25mg/kg/day Q6hrs (side effects: hirsutism, edema, hyperuricemia, electrolyte disturbances, advanced bone age, IgG def)
2. octreotide 20-50 mcg sc Q6-12 hr.
   side effects: vomiting, diarrhoea, hepatic dysfn, poor growth due to GH inhibition.
3. calcium channel blockers can be tried.
4. glucagon, hydrocortisone also be useful.

SURGERY- partial or subtotal pancreatectomy.


Hypoglycemia should be anticipated and treated aggressively.

Term, macrosomic baby, in non-diabetic mother, recurrent hypoglycemia – think of possibility of Congenital hyperinsulinism.

Always do critical sample as it is crucial for further management.
THANK YOU
Pancreatic \( \beta \) cells react to hypoglycaemia by inhibiting insulin release and the fall in insulin concentration within the islet are responsible for release of glucagon from adjacent \( \alpha \) cells.

Recent evidence suggests that the trigger for the major physiological response to hypoglycemia is located within the hypothalamus.
Physiological protection against hypoglycaemia
Major components of the counter regulatory and sympathetic responses to hypoglycemia

- Hypoglycaemia
- Hypothalamus
- Pituitary
- Sympathetic outflow
  - Epinephrine
  - Sympathetic nerve activity
  - ACTH
  - Glucagon
  - Vasopressin
  - Growth hormone
  - Cortisol

- Gluconeogenesis
- Glycogenolysis
- Inhibition of insulin secretion

- Blood flow diverted to:
  - Brain
  - Muscle
  - Liver

- Rise in blood glucose