Approach to hypoglycemia in infants and children

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Objectives

- Definition.
- Causes:
  - Neonatal hypoglycemia.
    - Transient vs. Persistent
  - Childhood hypoglycemia.
- Investigations.
- Management.

- Discussion of 6 cases (endocrine causes of hypoglycemia)

Hypoglycemia

- One of the major metabolic emergencies at any age.
- Incidence: 1-3/1000 live births.
- Has potentially devastating consequences on brain development and cognitive functions.
- Is a heterogeneous disorder with many different possible etiologies, including hyperinsulinism, glycogen storage diseases, fatty acid oxidation defects, hormonal deficiencies, other inborn error of metabolism, drug poisoning, and others.

Major long term sequelae of recurrent hypoglycemia

- Physical and learning disabilities.
- Recurrent seizure activity.
- Cerebral palsy.
- Autonomic dysregulation.
- Neurodevelopmental delay.

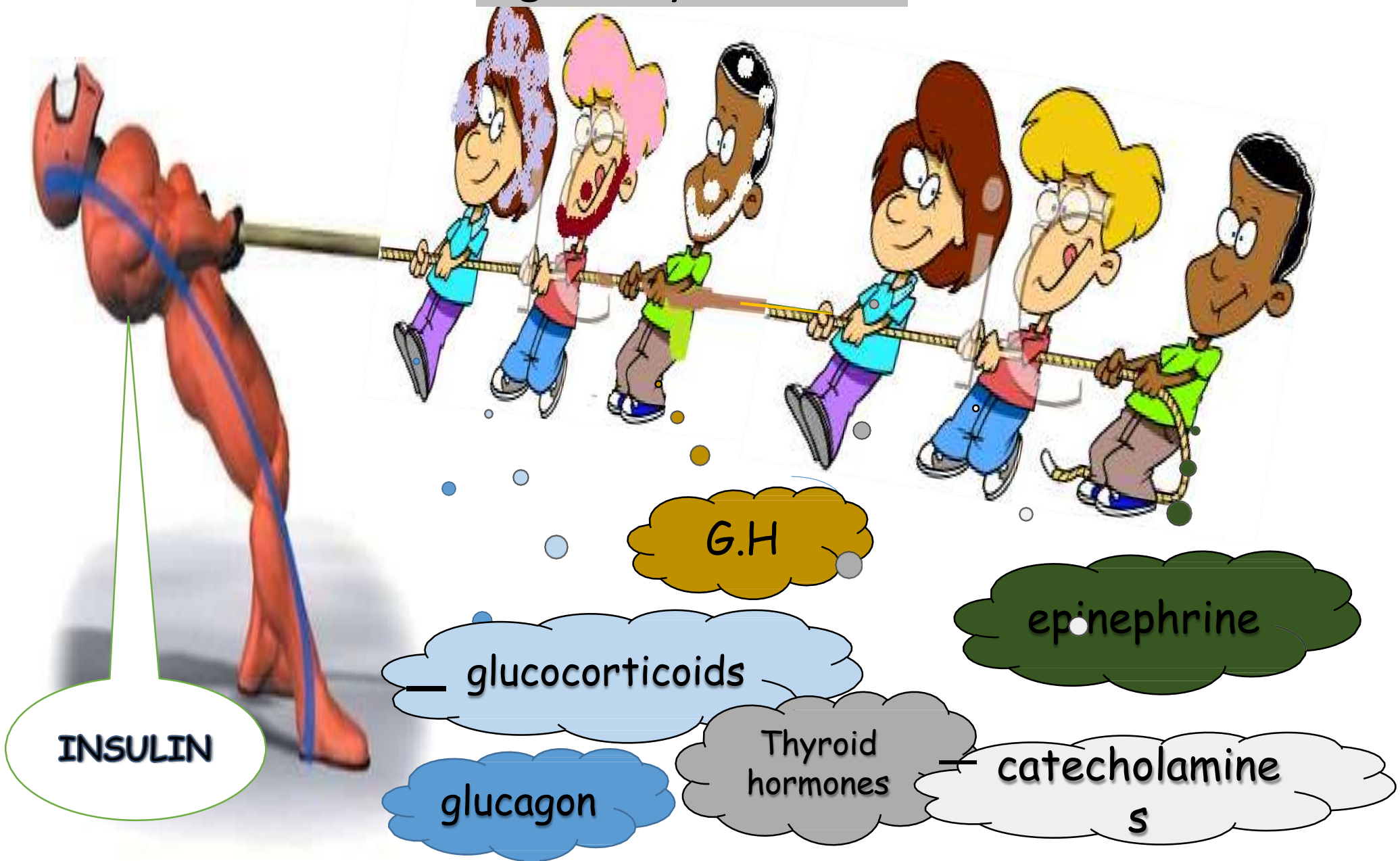
Given these severe consequences, the prompt diagnosis and appropriate management of hypoglycemic disorders in children are crucial.

Definition ??

- There is no definitive definition but most agreed definition is:
  - In neonates when plasma glucose concentration < 40 mg/dl (2.2 mmol/l).
  - In infants or children when plasma glucose concentration < 50 mg/dl (2.8 mmol/l).

Whole blood glucose value is 10- 15% less than plasma glucose.

Glucose homeostasis is made by balance between insulin & its counter regulatory hormones

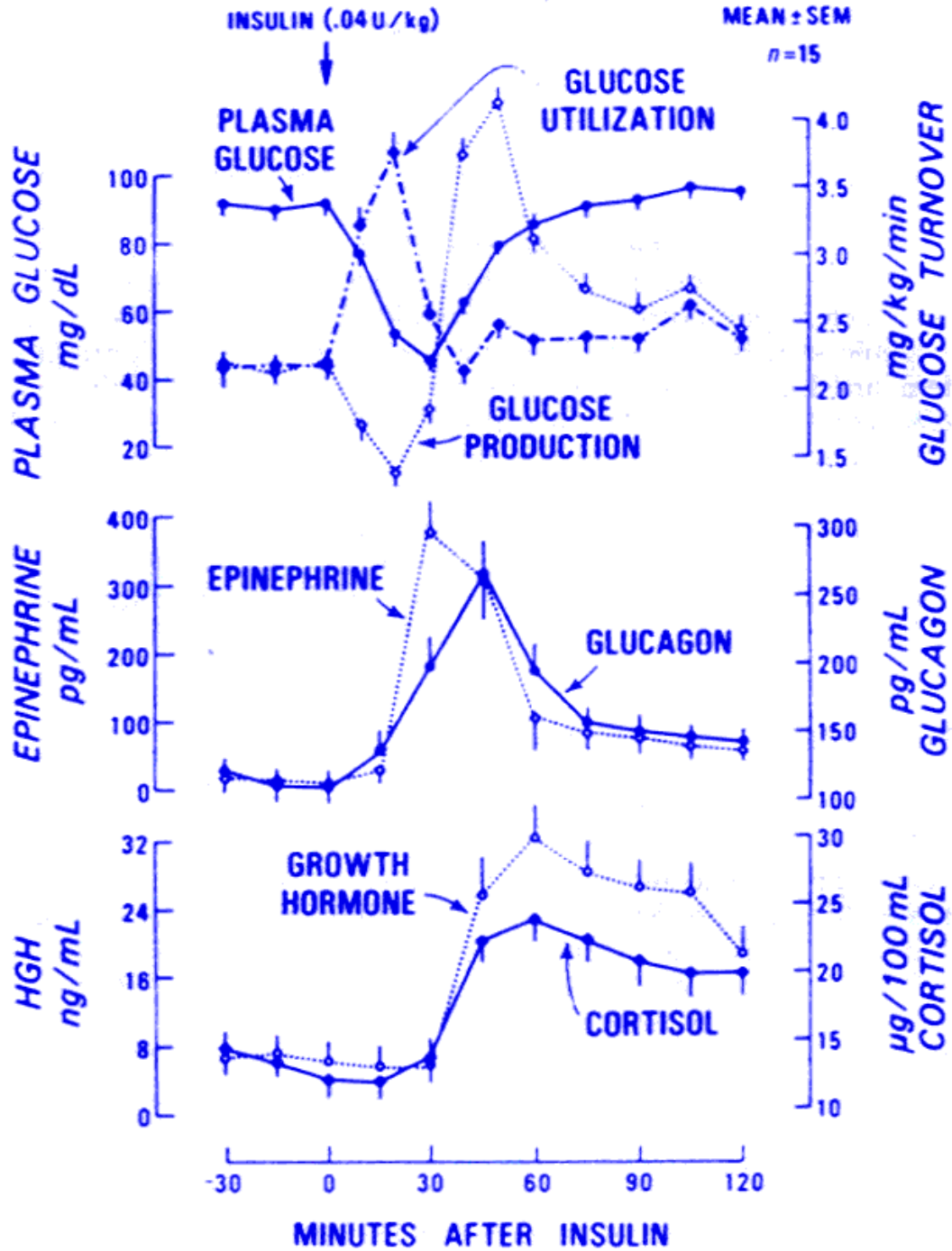


Counter-regulatory hormones

- Rapid acting hormones, are critical for counter regulation of the early phase of hypoglycemia.
  - Glucagon
  - Adrenaline
- The absence of the two hormones are not compensated by an even larger response of the other, and more severe hypoglycemia will follow.

Counter-regulatory hormones

- Slow – Acting hormones:
  - Growth hormone
  - Cortisol
- Their release will be starting 30 minutes post hypoglycemia and their counter –regulatory role is not appreciated until after 3 hours from the onset of hypoglycemia


INSULIN (.04 U/kg)
MEAN ± SEM
n=15
PLASMA GLUCOSE
GLUCOSE UTILIZATION
GLUCOSE PRODUCTION
PLASMA GLUCOSE mg/dL
mg/kg/min GLUCOSE TURNOVER
EPINEPHRINE
GLUCAGON
EPINEPHRINE pg/mL
pg/mL GLUCAGON
GROWTH HORMONE
CORTISOL
HGH ng/mL
µg/100mL CORTISOL
MINUTES AFTER INSULIN

Signs & symptoms

- In neonates (not specific signs & symptoms “sepsis –like”)
  - Lethargy.
  - Hypotonia.
  - Irritability.
  - Feeding difficulties.
  - Cyanosis.
  - Tachypnea /Apnea.
  - Hypothermia.
  - Seizure.
  - Coma.

Signs & symptoms

- Neurogenic (Adrenergic symptoms) are common (first stage symptoms):
  - Sweating.
  - Anxiety/ tremor / tachycardia.
  - Weakness.
- Neuroglycopaenic symptoms (become prominent when first stage is not corrected):
  - Headache / Irritability / Confusion.
  - Fatigue.
  - Abnormal behavior , amnesia.
  - Seizure / Coma.

Transient neonatal hypoglycemia

- Incidence 2 – 3 per 1000 live births.
- Occurs within first 12 hours after birth.
- Resolves within 3 – 5 days.

High risk group:

- Premature, SGA, twins.
- Respiratory distress, sepsis, birth asphyxia.
- Large birth weight .
  - Infant of diabetic mother.
  - Polycythemia.
  - Erythroblastosis fetalis.
  - hyperinsulinemia from islet cell hyperplasia

Persistent infantile /childhood hypoglycemia

- Incidence 5% of infants with hypoglycemia.
- Persistent (recurrent) hypoglycemia.
- Does not resolve within 5-7 days.

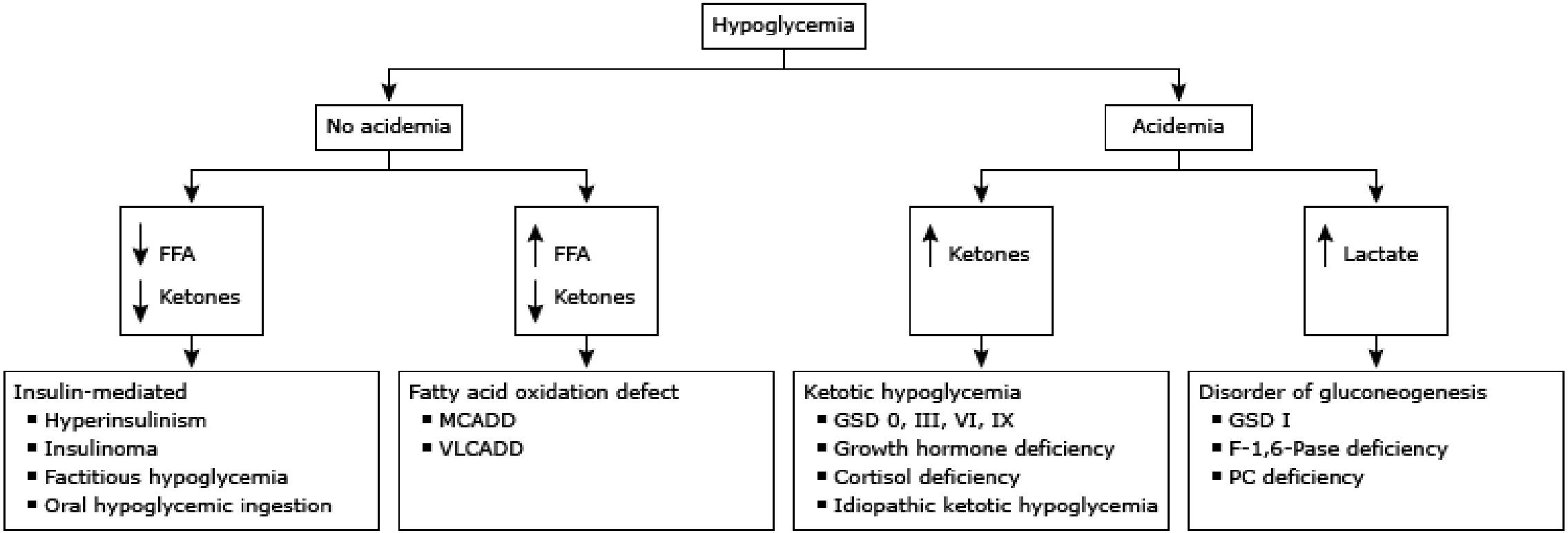
Causes:

- Hormonal deficiencies (15% of cases):
  - Panhypopituitarism (associated midline facial defect, micropenis, prolonged jaundice).
  - Isolated GHD.
  - ACTH / Cortisol deficiency
    - Primary adrenal insufficiency (CAH in neonate, Addison's in children or adolescents)
    - Secondary ACTH deficiency.

Persistent infantile /childhood hypoglycemia

- Hormone excess (hyperinsulinemia):
  - B - cell hyperplasia (neisidioblastosis (PHHI).
  - B - cell adenoma.
  - Beckwith-Weideman syndrome.
    - Macrosomia, macroglossia, microcephaly, ear-lobe fissures.
  - Substrate limited:
  - Ketotic hypoglycemia
- Inborn error of metabolism
  - Carbohydrate / amino acids/ organic acids / fatty acids
- Miscellaneous:
  - Drugs, sepsis, liver failure, …..etc.

Categorization of hypoglycemic disorders based on biochemical profile



Schematic representation of the biochemical profile obtained on the critical sample obtained during an episode of hypoglycemia. The biochemical profile helps to identify the pathophysiologic category of the underlying hypoglycemic disorder.

FFA: free fatty acid; MCADD: medium-chain acyl-CoA dehydrogenase deficiency; VLCADD: very-long-chain acyl-CoA dehydrogenase deficiency; GSD: glycogen storage disease; F-1,6-Pase: fructose-1,6-bisphosphatase; PC: pyruvate carboxylase.

Clinical assessments

- A careful medical history & examination:
  - History of prematurity, IUGR, infant of diabetic mother, birth asphyxia, polycythaemia or sepsis
  - Large baby might suggest Hyperinsulinism
  - Hypoglycemia that is triggered by certain component of diet may be indicative of inborn error of metabolism such as galactosaemia. MSUD,…….etc.
  - Cholestatsis and micropenis occur in setting of panhypopituitarism
  - Hepatomegaly in glycogen storage disease.
  - Myopathy in fatty oxidation defects & glycogen storage diseases.

Investigations

- Critical samples should be done during hypoglycemic episode (less than 50 mg /dl) or during fasting study>
  - Insulin and C- peptide assay.
  - Cortisol.
  - GH.
  - Ketone.
  - Lactate / pyruvate.
  - Ammonia.
  - FFA.
  - Urine specimen for:
    - organic acid
    - Ketone
    - Reducing substance

Glucagon stimulation test

- The glycemic response to glucagon provides an index of liver glycogen reserves.
- A glycemic response of ≥30 mg/dL is inappropriate, indicates excessive glycogen reserves, and provides indirect evidence of hyperinsulinism or insulin excess.
- This test is performed when the glucose is <50 mg/dL (2.8 mmol/L).
- Then, 1 mg of glucagon is administered intravenously or subcutaneously, and then plasma glucose is monitored every 10 minutes for a maximum of 40 minutes.
- If the plasma glucose increases by a <20 mg/dL increment during the first 20 minutes following glucagon administration, the test should be terminated and the child fed.
- If the plasma glucose increases by ≥30 mg/dL within 40 minutes after glucagon administration, this is considered an inappropriate glycemic response and is consistent with an insulin-mediated hypoglycemic disorder.
- If the plasma glucose increases by <30 mg/dL within 40 minutes after glucagon administration, an insulin-mediated hypoglycemic disorder is unlikely.

PHHI

Persistent Hyperinsulinemic Hypoglycemia of Infancy

Genetics of PHHI

- Is the most common cause of persistent hypoglycemia in neonates & infants.
- It is also referred to as congenital hyperinsulinism (CHI), familial hyperinsulinemic hypoglycemia, or primary islet cell hypertrophy (nesidioblastosis).
- The estimated incidence in Saudi Arabia is 1: 2, 500 because of a high rate of consanguinity.
- Mutations in the ABCC8 and KCNJ11 genes (SUR/Kir 6.2) are the most common and account for 40 to 45% of all cases (82% of diazoxide-unresponsive patients).
- Mutations have been identified on six other genes in approximately 5 to 10% of the cases.
- The genetic etiology for the remaining 45-55% of patients is still unknown.
- If patient is diazoxide-unresponsive either:
  - focal form of PHHI in 55-60% or
  - 40-45% are diffuse autosomal forms (SUR/Kir 6.2).

Persistent Hyperinsulinemia Hypoglycemia of Infancy (PHHI)

- Incidence 1:40,000 - 50,000 in the general population.
- Incidence as high as 1:2500 in Saudi Arabia (high consanguinity).
- Onset of symptoms is from birth to 18 months of age.
- Macrosomia at birth, reflecting the anabolic effects of insulin in utero.
- Increasing appetite & demands for feeding, wilting spells, jitteriness, and frank seizures are the most common presenting features.

Clues to suspect hyperinsulinism

- Rapid development of fasting hypoglycemia within 4 hours of fasting.
- Need high rates of glucose infusion to prevent hypoglycemia >10 mg/kg/min.
- Absence of ketonemia or acidosis.
- Elevated C-peptide or insulin levels at the time of hypoglycemia.
- The insulin (µU/mL):glucose (mg/dL) ratio is commonly > 0.4.
- Low levels of β - OH butyrate & FFA.

How to calculate GIR

A simplified formula for GIR calculation is

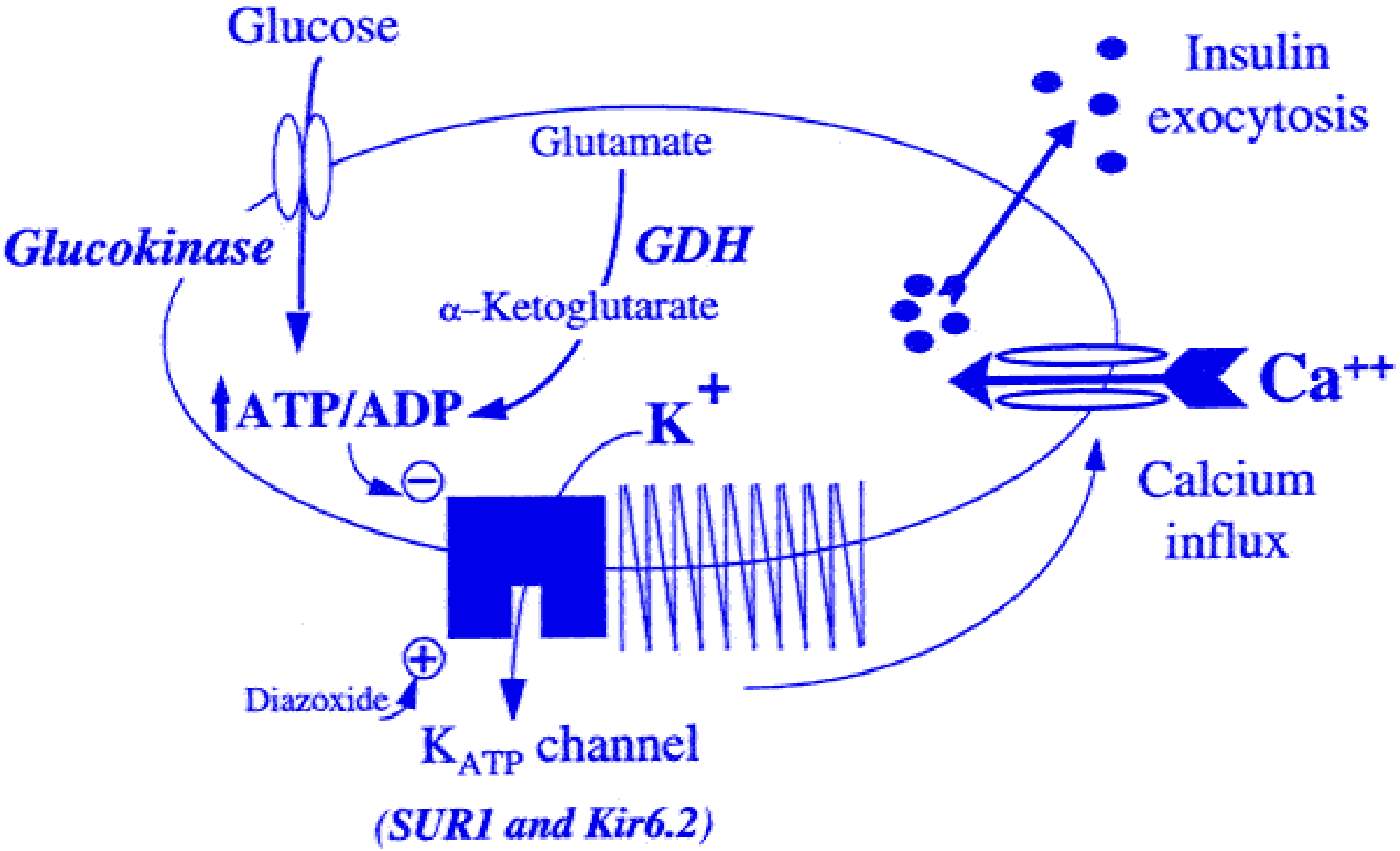
$$\frac{\%\ \text{dextrose} \times \text{ml/kg/day}}{144}$$

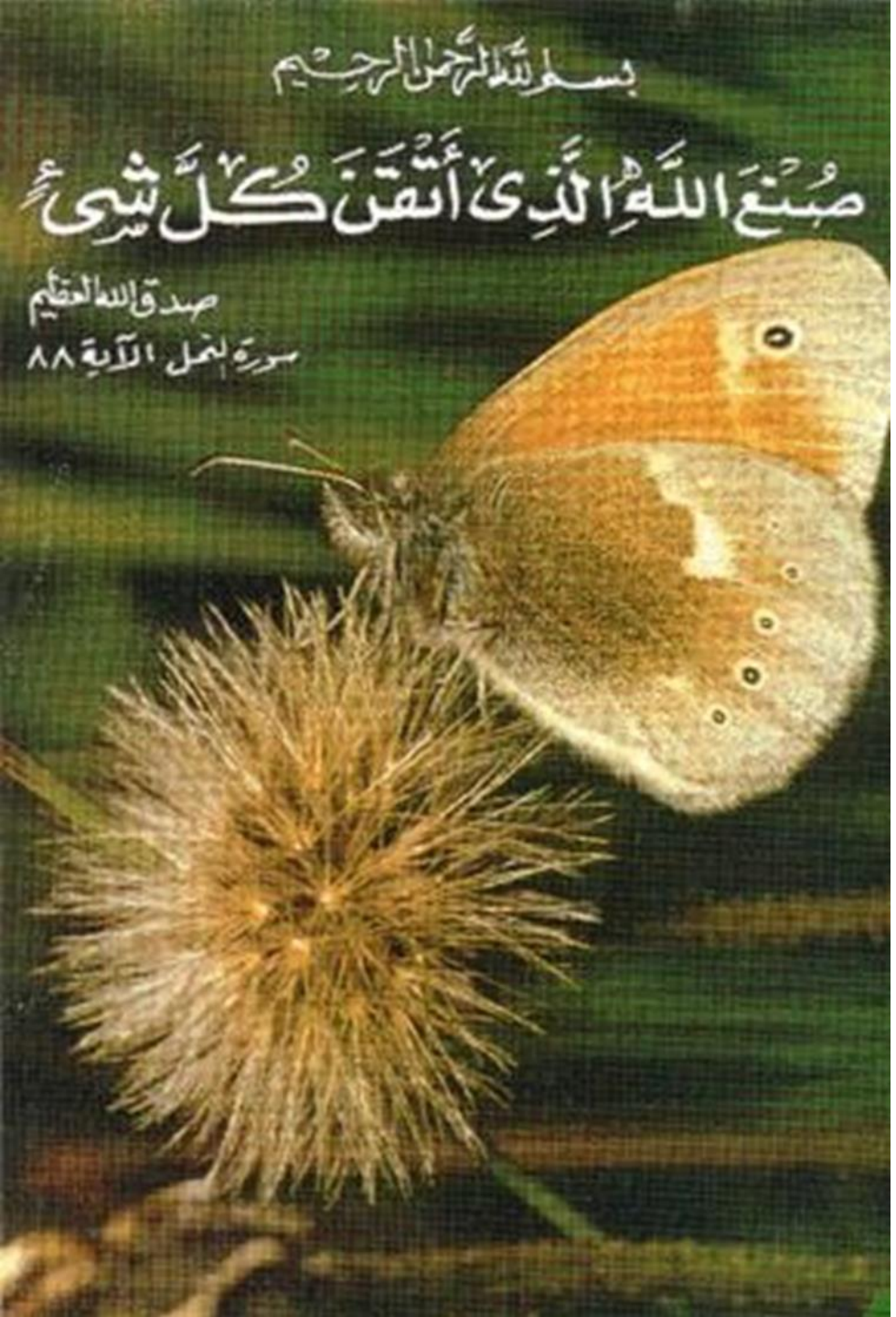
For example- a day 1 neonate receiving 60ml/kg/day of 10% dextrose has a GIR of:

$$\frac{\%\ \text{dextrose (10)} \times \text{ml/kg/day (60)}}{144} = 4.2\ \text{mg/kg/min}$$

β- Cell regulation of insulin secretion

- Glucose enters the cell via glucose transporter 2 (GLUTR 2) which is not rate limiting for glucose metabolism.
- Once inside the cell, glucose is converted to (G_6P) by enzyme Glucokinase (GKS).
- Increase energy production increases the ratio of ATP to ADP +Pi
- The increased ratio, normally closes the K_{ATP} channel which leads to depolarization of the β- cell plasma membrane, then Ca - channel open
- Increased intracellular Ca, leads to fusion of the insulin containing vesicles and then releasing of insulin


Glucose
Insulin
exocytosis
Glutamate
Glucokinase
GDH
α–Ketoglutarate
ATP/ADP
K+
Ca++
Calcium
influx
Diazoxide
KATP channel
(SUR1 and Kir6.2)



β- Cell dysregulation of insulin secretion

- Glucokinase enzyme (GCK)
  - Gain of function mutations in GCK leads to Hyperinsulinism (AD) .
  - Loss – of – function mutation in GCK leads to β-cell insensitivity to extra cellular glucose, with subsequent development of MODY 2.

PHHI

- 95% of cases are sporadic.
- Rare familial forms are caused by recessive or dominant defects in 4 different genes on 11p15.1
  - Sulphonylurea SUR1 gene.
  - Glutamate dehydrogenase (GLUD-1) gene.
  - Glucokinase (GK) gene.
  - KIR 6.2 : potassium channel inward gene.

Hypoglycemia management

Parenteral dextrose infusion

- Intravenous (IV) bolus of dextrose, is given over 5 - 15 minutes (2 – 4 mL/kg of 10 % dextrose), followed by continuous administration of dextrose (GIR normally of 5 - 8 mg/kg/ min).
- If GIR exceeds 10 mg/kg/min (suggestive of hyperinsulinism).
- The maximum dextrose concentrations through peripheral IV catheter or a low lying umbilical venous catheter is 12.5 %.
- Maximum dextrose through central venous catheter is 25 %.

Management

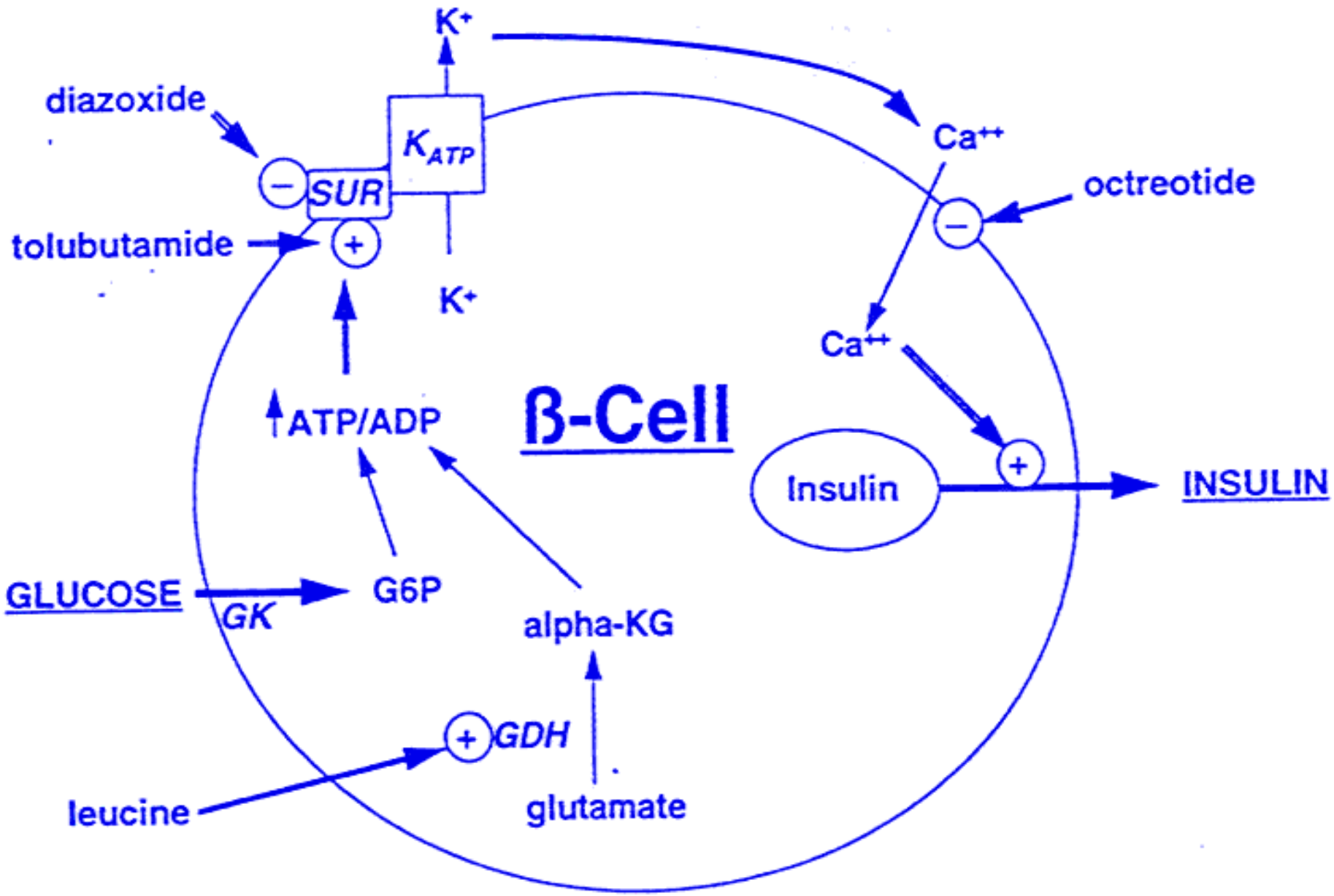
Medical

- Glucagon infusion
- Diazoxide
- Somatostatin analogue

Patients with SUR 1 / KIR 6.2 gene mutation usually doesn't respond to Diazoxide

- Surgical
  - Focal adenoma excision
  - 75 % pancretectomy
  - Near-total (95%) pancretectomy

Medical treatment of hyperinsulinism



Diazoxide

- Acts by inhibiting insulin secretion at SUR1.
- The starting dose is 10 mg/kg, may be increased to 20 mg/kg/day on 3 divided doses.
- Adverse reaction:
  - Hypertrichosis.
  - Hyperuricemia.
  - Salt and water retentions.
  - Hyperglycemia & ketoacidosis during illness.

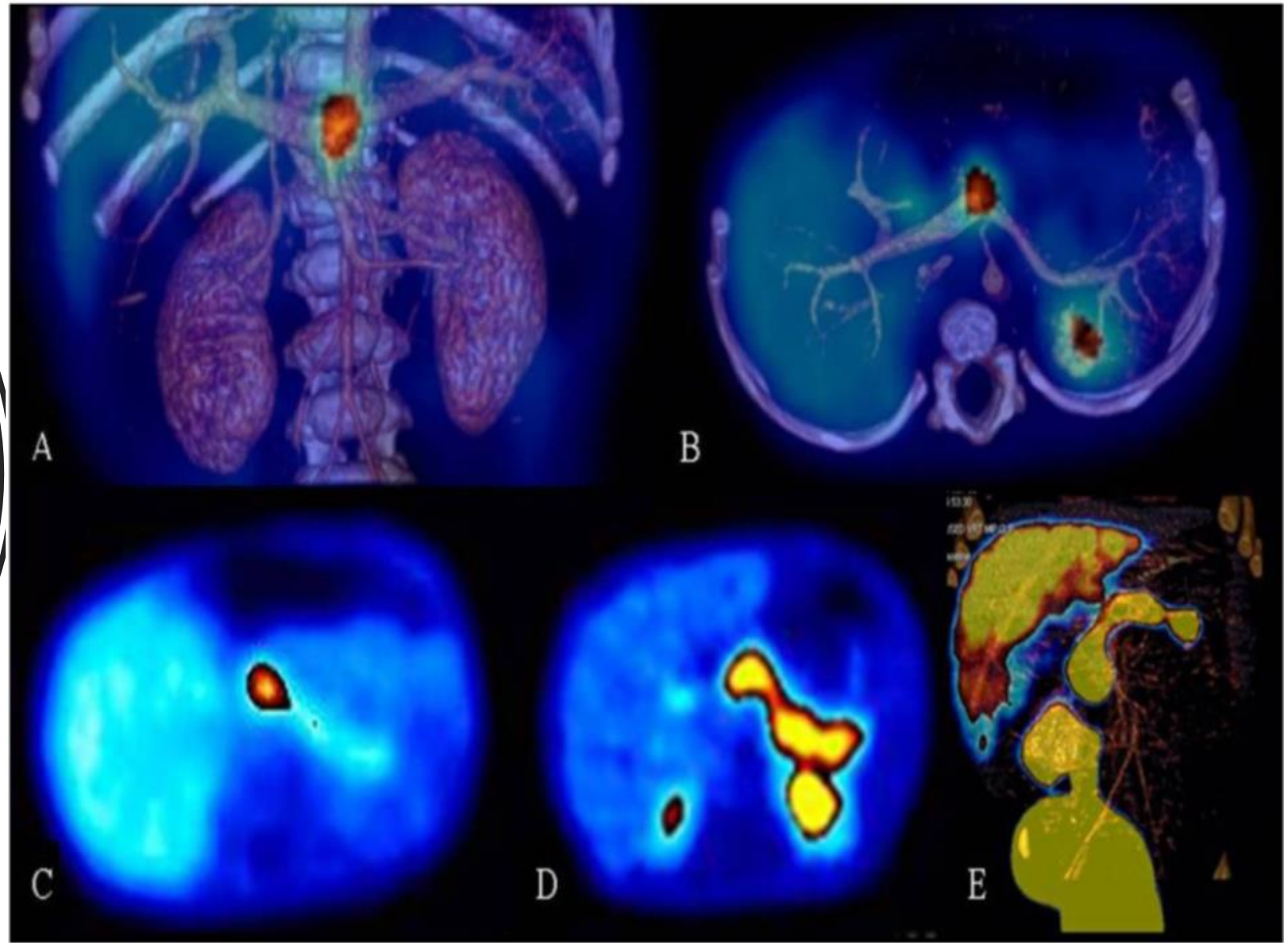
Patients with SUR 1 / KIR 6.2 gene mutation usually doesn't respond to Diazoxide

Octreotide

- Long acting Somatostatin.
- Inhibits insulin secretion at the level of calcium channel
- Dose of 5-25 µg/kg/day divided into 2-3 doses.
- No clear maximum dose has been established for these children with hyperinsulinism.
- Adverse effects:
  - Nausea
  - Steatorrhea
  - Delayed growth
  - gall stone formation

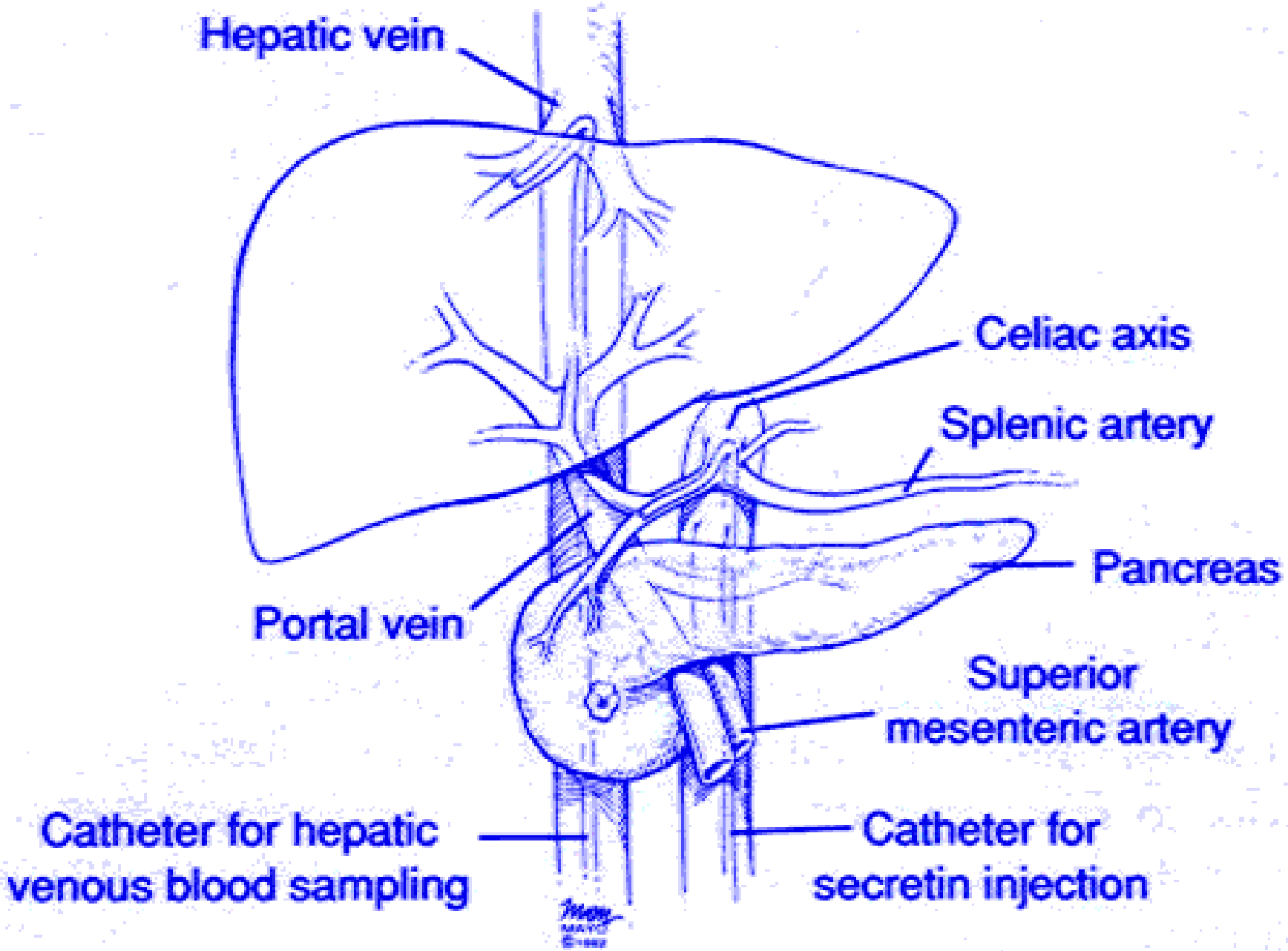
Last option is subtotal pancreatectomy

we need to differentiate between diffuse β-cell hyperplasia or focal β-cell microadenoma by doing Positron emission tomography using 18-fluoro-ldopa DOPA-PET scan



A, B, C are focal forms
D, E are diffuse forms

Pre-operative selective venous sampling



Conclusion

- Early diagnosis and aggressive management of hyperinsulinemia hypoglycemia is the cornerstone for prevention of hypoglycemia induced neuronal injury.
- High index of suspicion, early diagnosis and aggressive management is essential to prevent brain injury due to hypoglycemia.
- Severe brain damage is the consequence of deep and prolonged hypoglycemia presenting as coma and/or status epilepticus in neonates.
- In older children, hypoglycemia are usually less severe and brain damage is less frequent.
- Psychomotor skills and neurological disabilities with intellectual impairment is usually sequel.
- Very important to diagnose and treat hypoglycemia in order to avoid all mentioned sequel.

Various cases study on hypoglycemia

Case # 1

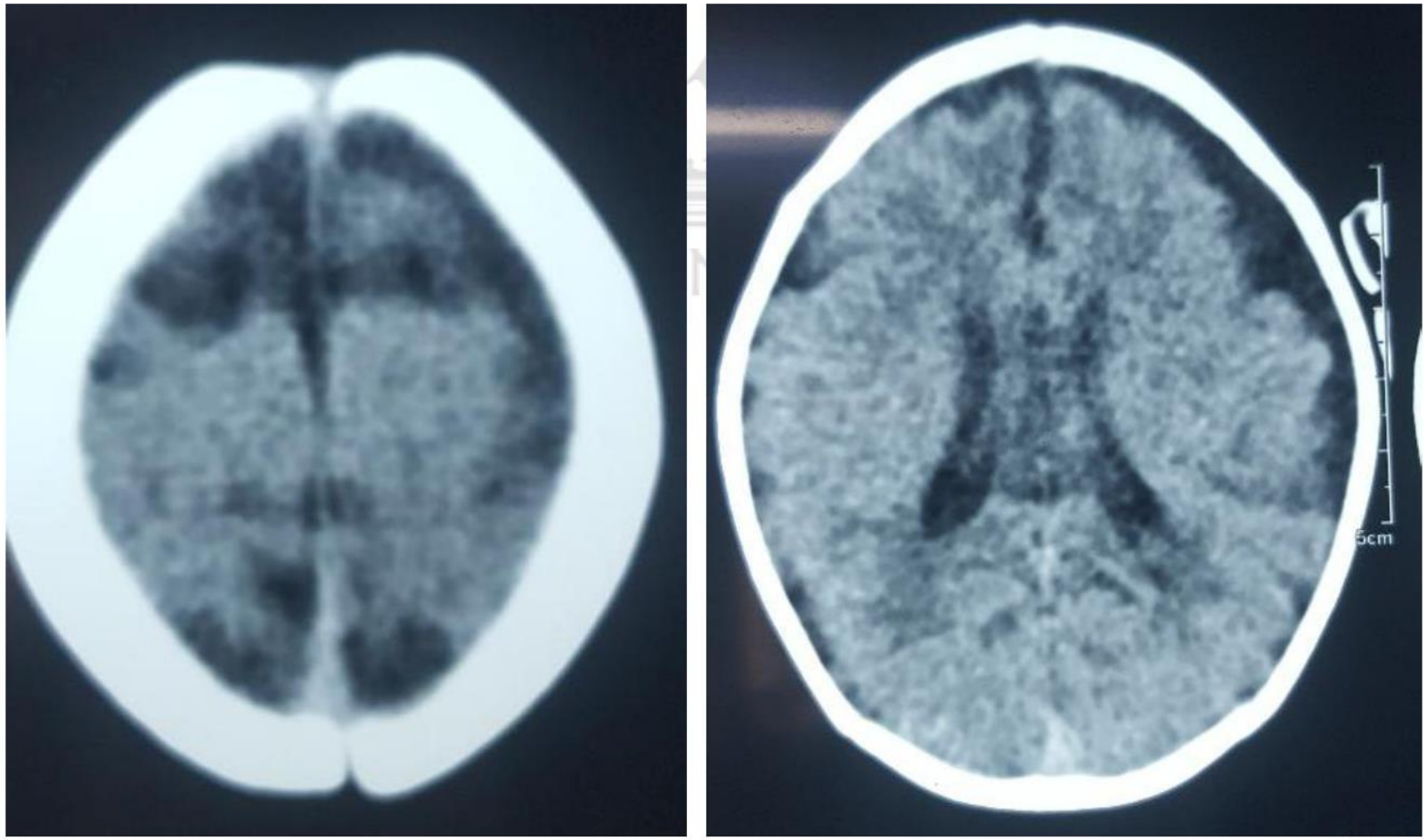
- Three months old girl of first degree consanguineous parents was born by cesarean section at 38th week at term after an uneventful pregnancy.
- Birth weight was 4500 g.
- Apgar scores were 10 at 1 minute and 5 minute.
- She was admitted at the age of three months with the complaints of repeated seizure since age of 20 days.
- During seizure, her blood glucose found low and seizure resolved by glucose administration.
- Initially, seizure was generalized tonic-clonic in nature and last six weeks she developed flexion of head over trunk and seizures episode were about 100 times day, and even in sleep.

- On examination, her weight was on 90th %, length and occipitofrontal circumference was on 25th %.
- She had global developmental delay.

What else you need to ask and need to examine?

Investigations

- Her random blood glucose was 1.2 mmol/L
- Critical blood sample done when blood glucose was1.4 mmol/L:
  - Serum insulin was 8.8 µU/ml.
  - Serum insulin : glucose ratio was 6.28 (N < 0.3),
  - growth Hormone was 10.7 ng/ml (N,>7-10 ng/ml),
  - TSH was 3.6 mU/L (N, 0.05-5mU/L), FT4 was 20.5 pmol/L(N; 8-26 pmol/L)
  - Cortisol was 635 nmol/L (N; 140-690mmol/L).
- Plasma ammonia and ABG was normal.
- Urine for ketone body and reducing substance was nil.
- EEG showed focal epileptiform discharges over left frontal, central and temporal regions and background electrophysiological function was disturbed.
- Genetic analysis was not available.



CT scan showing dilatation of ventricles increased subarachnoid space and cortical atrophy

Clues to the diagnosis PHHI

- First degree consanguinity of marriage in parents of our patients as it an autosomal recessive disorder.
- large for gestational age, these infants are characteristically large due to the growth- promoting action of insulin.
- Symptoms of hypoglycemia appear in first 3 months of life.
- Insulin & C-peptide levels are inappropriately elevated compared to hypoglycemia.
- low levels of free fatty acids and ketones can be observed due to inhibition of lipolysis.

Case # 2

- A 7-year-old girl was admitted to the hospital due to episode of unconsciousness following a fall from a scooter.
- Her blood glucose was 46 mg/dL and urine ketones were positive.
- She regained consciousness after treatment with intravenous glucose.
- It turned out that six months earlier she had seizures and blood glucose 39 mg/dl during a febrile illness treated in intensive care unit.
- Analysis of her cerebrospinal fluid ruled out meningitis, & electroencephalogram was normal.
- She started to be fatigued, decreased appetite, and increased irritability were noted by parents since age 6 years.

What else you need to ask for in history??

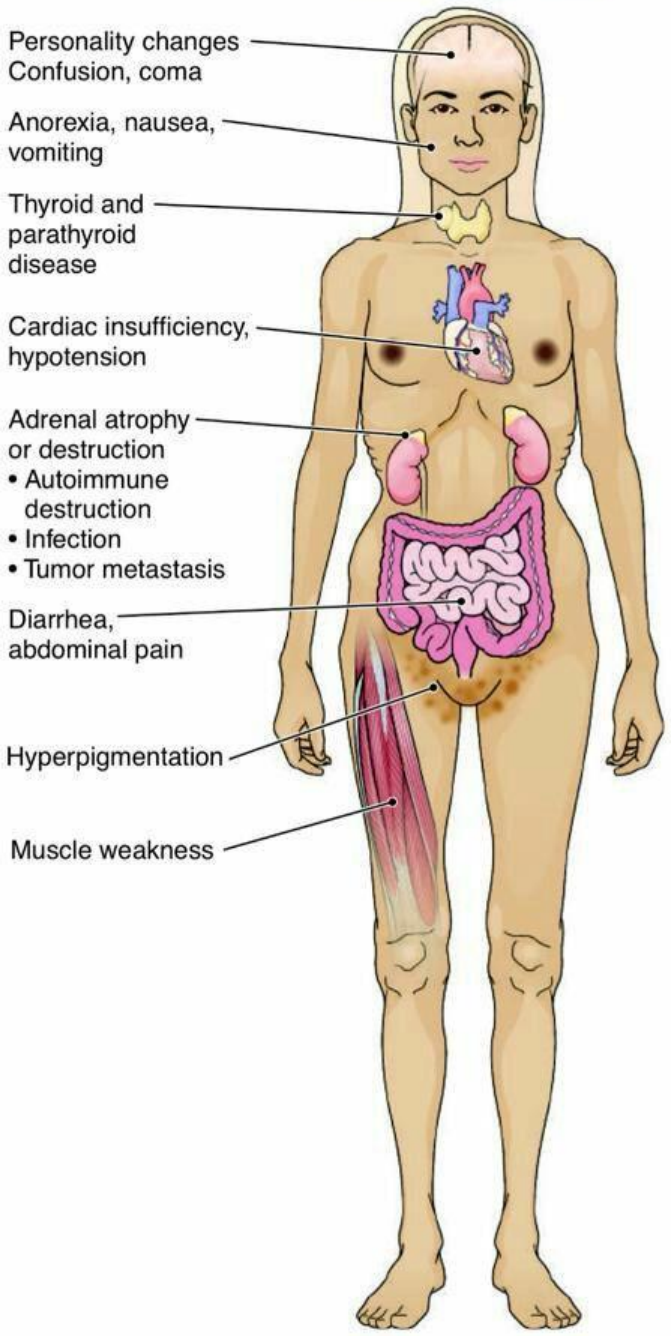
- Height was 140 cm + 1.8 SDS), weight 20 kg (-1.7 SDS), and BMI 11.9 kg/m^2 (-2SDS).
- BP was 65/43, HR 110/minute, RR 20 /minute, Temperature was 36.5.

What else you need to look for?

Investigations

- TSH was 2.20 mU/L, free T4 1.67 ng/dL, T3 1.42 ng/mL (all normal).
- ACTH was 85 pg/mL (high), cortisol 110 mmol/l (low), DHEAS <15 ug/dL (low)
- IGF-1 296 ng/ml.
- Plasma renin activity 260 ng/mL (high), Aldosterone low and normal serum electrolytes.
- Repeat morning ACTH was < 5 pg/mL & cortisol 220 ug/dL.
- ACTH stimulation test showed cortisol 160 ug/dL at 45 min after Cortrosyn 0.250 mg injection.
- Adrenal autoantibodies were positive.

Addison's disease



Management of adrenal insufficiency

- Life - long replacement of glucocorticoid therapy.
- For primary AI other than CAH, hydrocortisone at 8–12mg/m2 /day in 3 divided doses is recommended.
- For CAH, the consensus dosing is 10–15mg/m2 /day.
- Patients with secondary AI may be maintained on 6-8 mg/m2/day. Doses usually adjusted according to the clinical symptoms and ACTH level.
- Requirement for glucocorticoid increases with stress (fever, vomiting, diarrhea, surgery & anesthesia) to 2-3 times the usual doses.

Case # 3

- A 28 day old phenotypic female infant was admitted for poor weight gain and lethargy.
- FT BW 3250 gm, length 51 cm, HC 34 cm
- Lethargic, depressed fontanelle.
- mild dehydration and decreased skin turgor.
- mild hyperpigmentation, including oral cavity.
- External genitalia seemed normal female type with no ambiguity.

- Her body weight, length & HC were 2900, 51 cm and 33.5 cm, all < 5th centiles.
- T: 37.1°C. BP 60/40 mmHg, RR 39/min, PR 112/min

Laboratory findings

- Sodium was 129 mmol/l, potassium was 6.1 mmol/l
- RBS: 45 mg/dl; BUN: 2 mmol/l; creatinine 18 (normal)
- CRP: negative; blood culture: negative.
- ABG: pH: 7.3 HCO3=11.9 mmol/L, PCO2= 35 mmHg
- Hormonal assay: Cortisol: 98 mmol/l, ACTH: >1000 pg/ml, 17 OHP: 78 ng/ml.

What else you need to know or to do more?

Final diagnosis is CAH

Case # 4

- Three year old boy, previously healthy was brought to the emergency room with history of fainting episodes preceded with sweating.
- Past history of transient neonatal hypoglycemia resolved by age of 2 days.
- His fainting attack was the first time, but previously had some sort of on/ off dizziness.
- When he was fainted, his blood pressure and vital signs were normal.
- Child appeared drowsy and lethargic.
- His blood glucose at time of fainting was 43 mg/dl.
- He picked up immediately after having intravenous glucose infusion.
- His systemic examination is completely normal healthy boy with normal growth parameters.

What else you need to know more??

Investigations

- random blood glucose was 43 mg/dl.
- Critical blood sample done when blood glucose was 43 mg/dl:
  - Serum insulin was 0.4 µU/ml.
  - Serum insulin : glucose ratio was 0.2 (N < 0.3),
  - growth Hormone was 13 ng/ml (N,>7-10 ng/ml),
  - TSH was 2,7 mU/L (N, 0.05-5mU/L), FT4 was 14.5 pmol/L(N; 8-26 pmol/L)
  - Cortisol was 535 nmol/L (N; 140-690mmol/L).
- Plasma ammonia and ABG were all normal.
- Urine for ketone body was ++++.
- Liver function test was normal.

What other 2 important investigations to confirm the diagnosis??

Ketotic Hypoglycemia

- Most common form of childhood hypoglycemia.
- Presents between the ages of 18 months & 5 years.
- Remits spontaneously by the age of 8-9 yr.
- Represents abnormally shortened fasting tolerance.
- Hypoglycemic episodes typically occur during periods of intercurrent illness when food intake is limited.
- At the time of documented hypoglycemia, there is associated ketonuria, ketonemia & elevated FFA.
- serum alanine level is low & is diagnostic.

- Child usually appears lethargic, drowsy, dehydrated.
- seizures & coma are uncommon.
- The levels of counteregulatory hormones are appropriately elevated, and insulin conc. are appropriately low, ≤5-10 µU/mL
- Plasma alanine concentrations are markedly reduced after an overnight fast and decline even further with prolonged fasting.
- Alanine is the only amino acid that is significantly lower in these children
- Infusions of alanine (250 mg/kg) produce a rapid rise in plasma glucose.

- Etiology is usually defect in any of the complex steps in oxidative deamination of amino acids (Alanine synthesis, or alanine efflux from muscle).
- Immaturity of ANS may have a role.
- patient is smaller than age-matched controls.
- History of transient neonatal hypoglycemia
- Spontaneous remission is explained by the increase in muscle bulk with its resultant increase in supply of endogenous substrate and the relative decrease in glucose requirement per unit of body mass with increasing age.

- Treatment: frequent feedings of a high protein, high-carbohydrate diet.
- During intercurrent illnesses, parents should be taught to test urine for ketones(precedes hypoglycemia by several hours)
- In the presence of ketonuria, liquids of high carbohydrate content should be given.
- If not tolerated, the child should be treated with intravenous glucose administration.

Case # 5

- Four – day old boy, with birth weight of 4.5 kg.
- Normal antenatal & natal histories.
- Good Apgar score.
- Not infant of diabetic mother.
- Parents are not relatives.
- He developed seizure at 3 days of age because of repeated hypoglycemic attacks (lowest RBS reading was 32 mg/dl).
- His general look (photo).

Questions ??

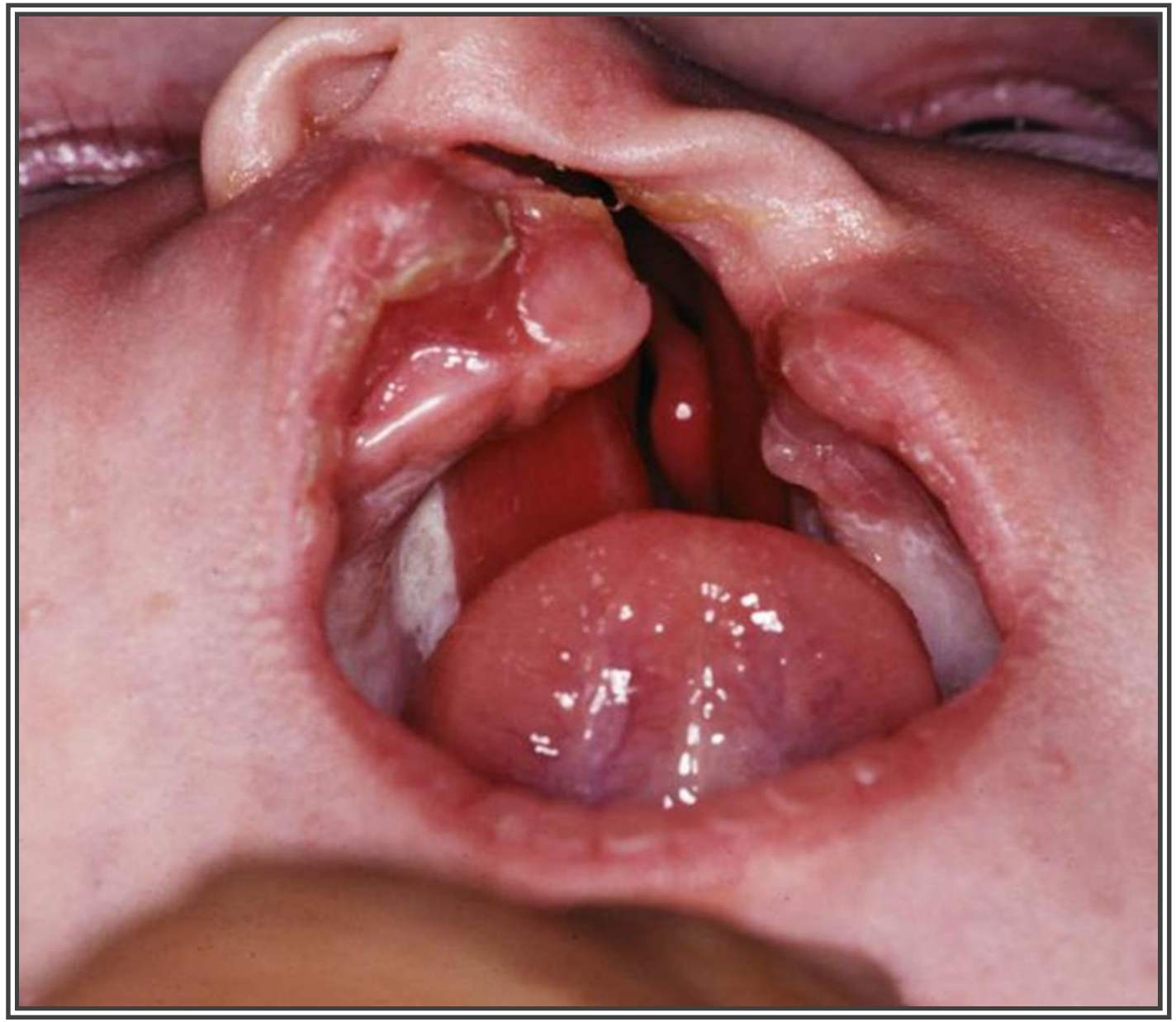
1. What abnormal finding you could see?
2. What important physical examination you are going to do?
3. What important investigation to confirm diagnosis?
4. What important investigations you are going to screen for associations.
5. What is the final diagnosis??

Beckwith-Wiedemann syndrome (BWS)

- BWS is an overgrowth syndrome.
- Is genetically heterogeneous disorder that involves an imprinted region of chromosome 11p15.
- Characterized by:
  - Antenatal & postnatal overgrowth.
  - Macroglossia.
  - Hypoglycemia.
  - Hemihypertrophy.
  - Ear creases or pits
  - Abdominal wall defects (omphalocele).
  - Increased risk of embryonal tumors (Wilms’tumor & hepatoblastoma).
  - Mental retardation is uncommon and usually related to early hypoglycemia.

Question # 6

- One – day old boy, with birth weight of 2.5 kg, length 50 cm.
- Breach delivery.
- Normal antenatal & natal histories.
- Good Apgar score.
- Healthy mother during gestation.
- He developed seizure at 8 hours of age because of low glucose of 30 mg/dl as well he has lowish blood pressure with MAP of 22 mmgh.
- His general look (photo).



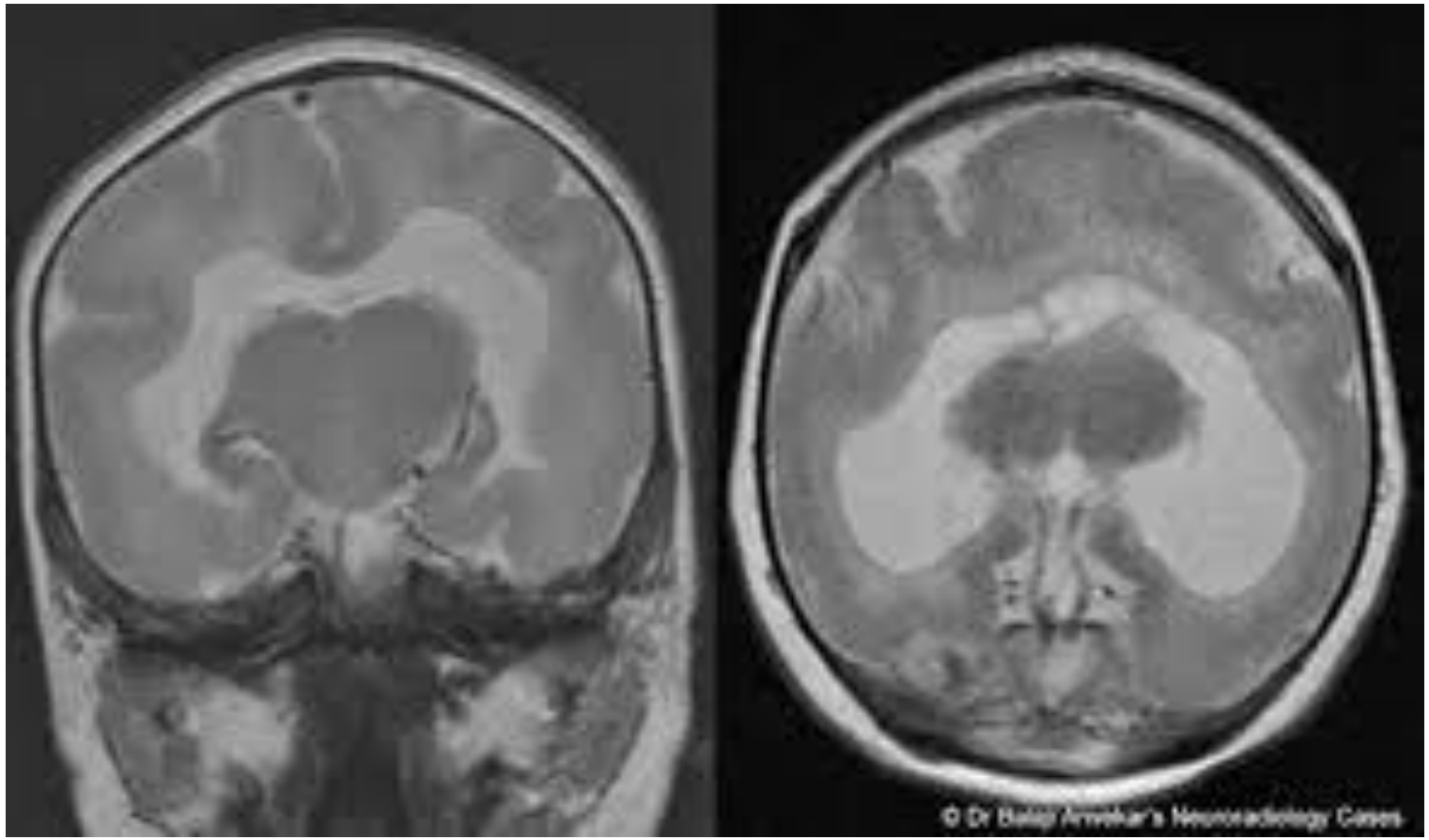
Questions ??

1. What abnormal finding you could see?
2. What other important physical examination you expected to find?
3. What important investigations you are going to screen for associations.
4. What do you think underlying cause of his hypoglycemia?

Hypopituitarism

- Most neonates with hypopituitarism have normal birth weights and lengths and no history of intrauterine growth retardation.
- However, they often have histories of breech presentation (particularly neonates with MPHD), although the explanation for this is unclear.
- The hypoglycemia risk is higher in neonates with hypopituitarism, with various manifesting symptoms, such as lethargy, jitteriness, pallor, cyanosis, apnea, or convulsions.
- Jaundice may be secondary to indirect hyperbilirubinemia (TSH deficiency) or to direct hyperbilirubinemia (GH or ACTH deficiencies).

MRI Brain was done. what is the diagnosis?



Holoprosencephaly (HPE)

- Is cephalic disorder in which the forebrain of the embryo fails to develop into two hemispheres.
- Normally, the forebrain is formed and the face begins to develop in the fifth and sixth weeks of gestation.
- The condition can be mild or severe.
- Most cases are not compatible with life and result in fetal death in-utero.
- When the embryo's forebrain does not divide to form bilateral cerebral hemispheres (the left and right halves of the brain), it causes defects in the development of the face , brain & pituitary structure and function.


Thanks