
به نام خدا

Diagnostic approach to Hypoglycemia in infants and children

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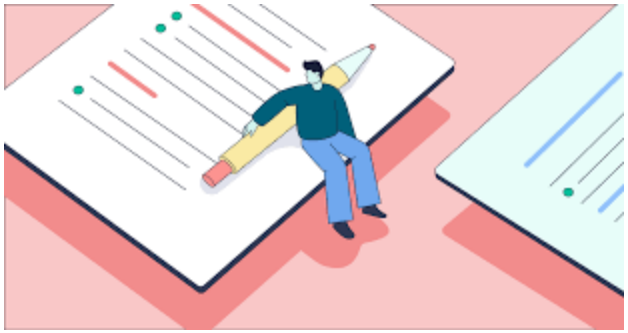
Outline

- Normal glucose homeostasis
- Hypoglycemia definition
- Clinical presentations
- History
- Examination
- Critical sample
- Interpretation of tests

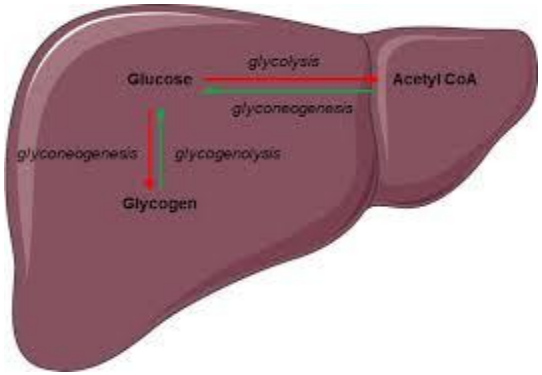


GLUCOSE HOMEOSTASIS IN NORMAL INFANTS AND CHILDREN

- In response to fasting :
- Insulin is suppressed and ↑ counterregulatory hormones
- These hormonal changes activate the three metabolic "fasting systems" (glycogenolysis, gluconeogenesis, lipolysis and ketogenesis)

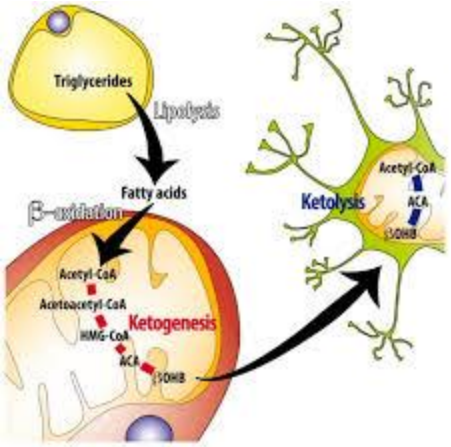
GLUCOSE HOMEOSTASIS IN NORMAL INFANTS AND CHILDREN

- Initially, during fasting, the liver is the primary source of glucose
- Generated through breakdown of glycogen and production of glucose via gluconeogenesis



GLUCOSE HOMEOSTASIS IN NORMAL INFANTS AND CHILDREN

- With more prolonged fasting, the body switches to adipose tissue as the major source of fuel
- Lipolysis and ketogenesis :↑ FFAs and the ketone bodies



GLUCOSE HOMEOSTASIS IN NORMAL INFANTS AND CHILDREN

- Glucose levels decline more rapidly and the transition to ketogenesis occurs earlier in infants and young children compared with older children and adults

GLUCOSE HOMEOSTASIS IN NORMAL INFANTS AND CHILDREN

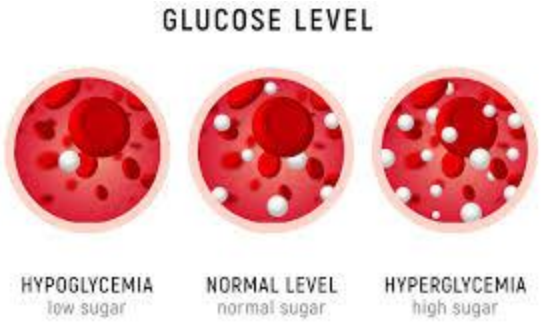
- The transition to ketogenesis occurs :
- fasting 12 to 18 hours in neonates and infants
- fasting 24 to 48 hours in older children and adults

Hypoglycemia

- Hypoglycemia is defined as a plasma glucose low enough to cause signs and symptoms of brain dysfunction
- Because the response to hypoglycemia occurs across a range of plasma glucose concentrations
- and signs of hypoglycemia are not reliably identifiable, especially in young children, and vary among individuals
- hypoglycemia cannot be defined as a single plasma glucose concentration

Definition

- After the first week of life, the normal range for plasma glucose is 70 to 100 mg/dL
- Diagnostic threshold : BS<50 mg/dL
- Treatment goal :maintain a plasma glucose >70 mg/dL

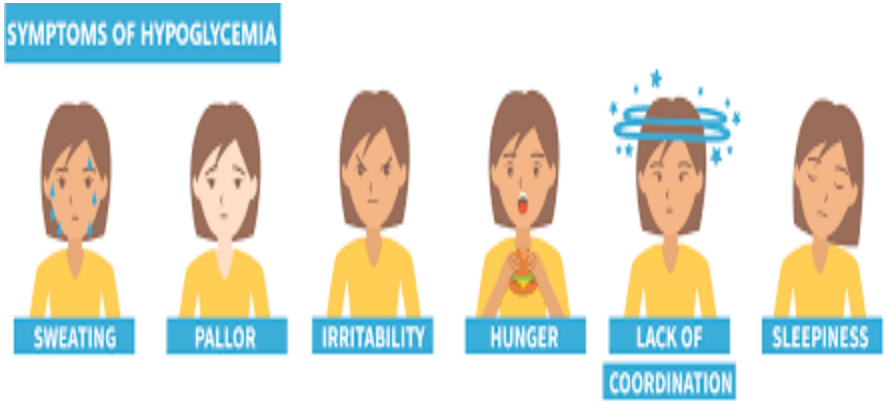


Clinical presentations

- Symptoms of hypoglycemia can be divided into neurogenic and neuroglycopenic symptoms:
- ●Neurogenic (autonomic) symptoms :
- Plasma glucose is less than 55 to 60 mg/dL
- Sweating , tremor, palpitations, tachycardia, and hunger

Clinical presentations

- ●Neuroglycopenic symptoms :
- Lethargy , confusion, irritability, loss of consciousness, and seizure
- Plasma glucose falls below 50 mg/dL



Whipple triad

- Older children and adults :

- Symptoms and signs consistent with hypoglycemia
- A documented low plasma glucose
- Resolution of the symptoms with normalization of the glucose concentration

Infants and toddlers

- Symptoms in these age groups are frequently nonspecific
- Irritability , lethargy, poor feeding, cyanosis, and tremor or jitteriness
- Commonly, infants manifest no symptoms of hypoglycemia until they present with a hypoglycemic seizure

Case 1

- شیرخوار 4 ماهه ای به دلیل تشنج بستری شده است .قند خون بیمار در بدو ورود 20mg/dlمی باشد.
- وزن تولد 3.8 کیلوگرم و وزن فعلی 7.5 کیلوگرم می باشد.
- در شرح حال و معاینه چه نکاتی اهمیت دارد؟

Case 2

- پسر 5 ساله ای به دلیل افت سطح هوشیاری توسط والدین به اورژانس آورده شده است.روز قبل اسهال و چند نوبت استفراغ داشته است.قند خون mg/dl42می باشد.
- وزن کودک 14 کیلوگرم می باشد .
- نکات مهم شرح حال و معاینه ؟

History and physical examination

History

- Age at presentation :
- Neonatal period and early infancy : Hyperinsulinism, disorders of gluconeogenesis, most inborn errors of metabolism and panhypopituitarism
- First two years of life : GSD, growth hormone or cortisol deficiencies
- Toddlers and young children : Ingestion, idiopathic ketotic hypoglycemia, GSD
- School-aged children and adolescents : Insulinoma, factitious hypoglycemia, other ingestions

History

- Triggers
- The details of the acute event should be carefully explored and should include feeding history, concurrent illness, and medication exposure

History

- Duration of fasting
- A short duration of fasting (several hours) : hyperinsulinism or GSD type I or III
- A longer duration of fasting (overnight) suggests a different GSD(types 0, VI, or IX), a disorder of gluconeogenesis, or idiopathic ketotic hypoglycemia

History

- Specific foods
- Symptoms after ingestion of milk products or fructose may indicate galactosemia or hereditary fructose intolerance, respectively

History

- Concurrent illness
- In children with unrecognized hypoglycemic disorders, the episodes are often triggered by illnesses
- Further evaluation is indicated for a child presenting with hypoglycemia during a noncritical, intercurrent illness

History

- For patients with critical illnesses, such as acute liver failure and sepsis, hypoglycemia is often a direct consequence of the illness rather than evidence of an underlying hypoglycemic disorder

History

- Ingestion
- The clinician must inquire about possible exposure to substances that cause hypoglycemia, such as oral hypoglycemic agents (sulfonylureas), ethanol, or beta blockers

History

- Perinatal history
- Birth weight, GA
- Whether the child had hypoglycemia at birth or in the neonatal period, including what type of treatment was necessary
- LGA : congenital hyperinsulinism or Beckwith-Wiedemann syndrome
- IUGR or SGA :perinatal stress-induced form of hyperinsulinism

History

- Results of NBS should be reviewed
- Important considerations include FAOD and galactosemia, in which hypoglycemia is a primary manifestation
- Hypoglycemia may also be an associated feature in some other inborn errors of metabolism

History

- Prior events
- It is important to explore the child's past medical history and to review available medical records to determine whether the child had other episodes suggestive of hypoglycemia

Family history

- Family members with a history of hypoglycemia or a monogenic form of diabetes suggest the possibility of a familial hyperinsulinemic disorder
- A family history of Reye syndrome, unexplained infant deaths, or unexplained hypoglycemic episodes

Physical examination

- Anthropometrics
- Short stature or poor linear growth :GHD or a GSD
- Tall stature :overgrowth syndrome, such as Beckwith-Wiedemann syndrome

Physical examination

- Anthropometrics
- Poor weight gain : GSD or a disorder of gluconeogenesis, hypopituitarism and ACTH deficiency or primary adrenal insufficiency
- Children who are underweight for age may also be at risk for idiopathic ketotic hypoglycemia

Physical examination

- Midline defects (eg, a single central incisor, optic nerve hypoplasia, cleft lip or palate, umbilical hernia) and microphallus or UDT may indicate hypopituitarism and/or GHD

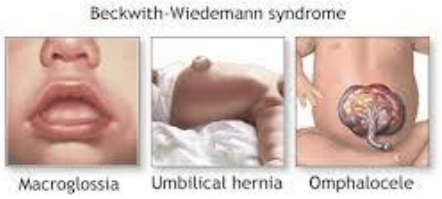
- Hepatomegaly is common feature of the GSD

Physical examination

- Macroglossia, abdominal wall defects, or hemihypertrophy : Beckwith-Wiedemann syndrome

- Hyperventilation :metabolic acidosis from an inborn error of metabolism or ingestion

- Hyperpigmentation : primary adrenal insufficiency



Case 1

- Age :infancy
- Overgrowth
- Lt:85th
- Hc=Nl
- Duration of fasting : short
- Seizure 1 week ago
- Development : near normal

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- وزن تولد 3.8 کیلوگرم و وزن فعلی 7.5 کیلوگرم می باشد.

Case 2

پسر 5 ساله ای به دلیل افت سطح هوشیاری توسط والدین به اورژانس آورده شده است.روز قبل اسهال و چند نوبت استفراغ داشته است.قند خون mg/dl42می باشد.
وزن کودک 14 کیلوگرم می باشد .

- Age:childhood
- Trigger:illness
- Duration of fasting :overnight
- Underweight ,Ht:10-25th
- History of hypoglycemia in neonatal period
- Normal development

Critical samples

- Evaluation for the majority of children presenting with hypoglycemia will require obtaining a "critical sample" of blood and urine at the time of hypoglycemia

Critical samples

- Plasma glucose
- Beta-hydroxybutyrate (BOHB)
- Comprehensive metabolic panel
- Insulin
- C-peptide
- Free fatty acids
- Lactate
- Ammonia

Critical samples

- Cortisol
- Growth hormone
- Acyl-carnitine profile
- Free and total carnitines

Critical samples

- Urine : The critical urine sample should be obtained at the same time and tested for organic acids
- The sample should also be tested for ketones if blood BOHB testing is not available

Interpretation

- When plasma glucose is <50 mg/dL , any detectable amount of insulin is abnormal
- C-peptide concentration ≥0.5 ng/mL

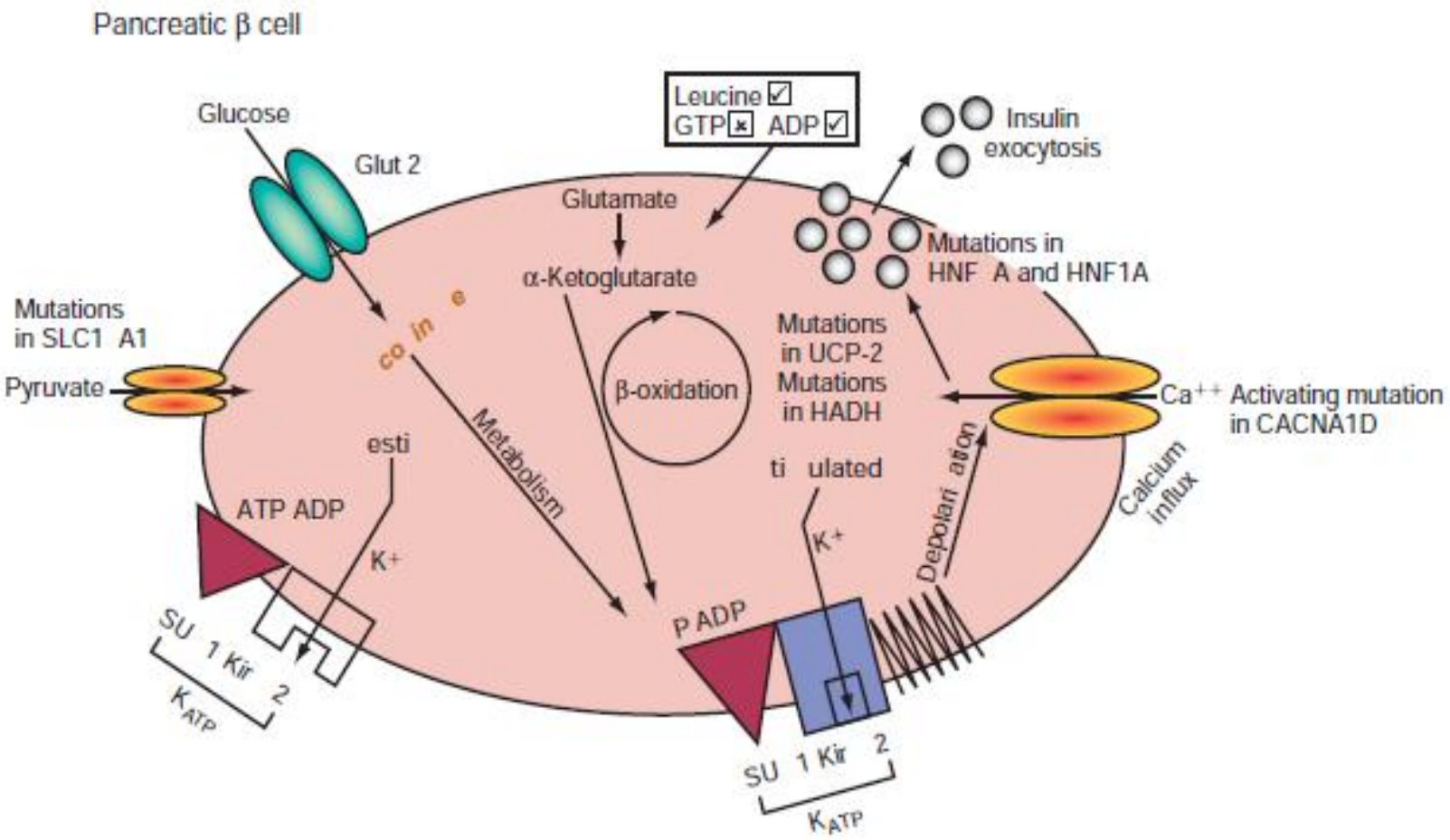
Hyperinsulinism

- Hyperinsulinemia :plasma insulin >2 μU/mL
- Hypofatty acidemia (plasma FAA<1.5 mmol/L)
- Hypoketonemia (plasma β-hydroxybutyrate <2.0 mmol/L)
- Inappropriate glycemic response to glucagon, 1 mg IV (change in glucose >40 mg/dL)

Hyperinsulinism

- The classic presentation of HI is at birth
- LGA
- Severe hypoglycemia, which requires a high glucose infusion rate: >10 mg/kg/min
- The clinical spectrum of HI is wide and patients may present with normal birth weight, require minimal dextrose support, or present outside of infancy

Insulin secretion in beta cells



High insulin with undetectable C-peptid

- Detectable insulin level with undetectable C-peptide :exogenous insulin administration
- Undetectable insulin level does not exclude this possibility
- Because not all laboratory assays detect the insulin analogs; a special assay may be required to detect certain insulin analogs

Detectable insulin and C-peptide levels

- Hyperinsulinism, sulfonylurea ingestion (accidental or deliberate), or insulinoma

Low ketones and elevated free fatty acids

- Fatty acid oxidation disorders
- The plasma acyl-carnitine profile helps identify the specific type of disorder

Elevated ketones with acidemia

- Elevated ketones and acidemia (bicarbonate <18 mmol/L) indicate a ketotic hypoglycemic disorder , which may be caused by several distinct mechanisms
- Acidemia may not be present in some cases

Elevated ketones with acidemia

- Disorders of glycogen metabolism :types 0, III, VI, and IX are characterized by ketotic hypoglycemia ,hyperlipidemia, and elevated liver function tests

Idiopathic ketotic hypoglycemia

- The most common form of childhood hypoglycemia
- This condition usually presents between ages 18 mo and 5 yr
- Remits spontaneously by 8-9 yr
- Hypoglycemic episodes typically occur during periods of intercurrent illness when food intake is limited

Idiopathic ketotic hypoglycemia

- The classic history is of a child who eats poorly or completely avoids the evening meal, is difficult to arouse from sleep the following morning and may have a seizure or may be comatose by mid-morning

Idiopathic ketotic hypoglycemia

- ketonuria and ketonemia
- Plasma insulin :appropriately low, ≤5 μU/mL
- 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 without causing significant changes in blood lactate or pyruvate

Idiopathic ketotic hypoglycemia

- Indicating that the entire gluconeogenic pathway from the level of pyruvate is intact, but that there is a deficiency of substrate
- This is a diagnosis of exclusion

Idiopathic ketotic hypoglycemia

- Children with ketotic hypoglycemia are frequently smaller than age-matched controls
- Often have a history of transient neonatal hypoglycemia
- Spontaneous remission observed in children at age 8-9 yr might be explained by the increase in muscle bulk

Hormone deficiencies

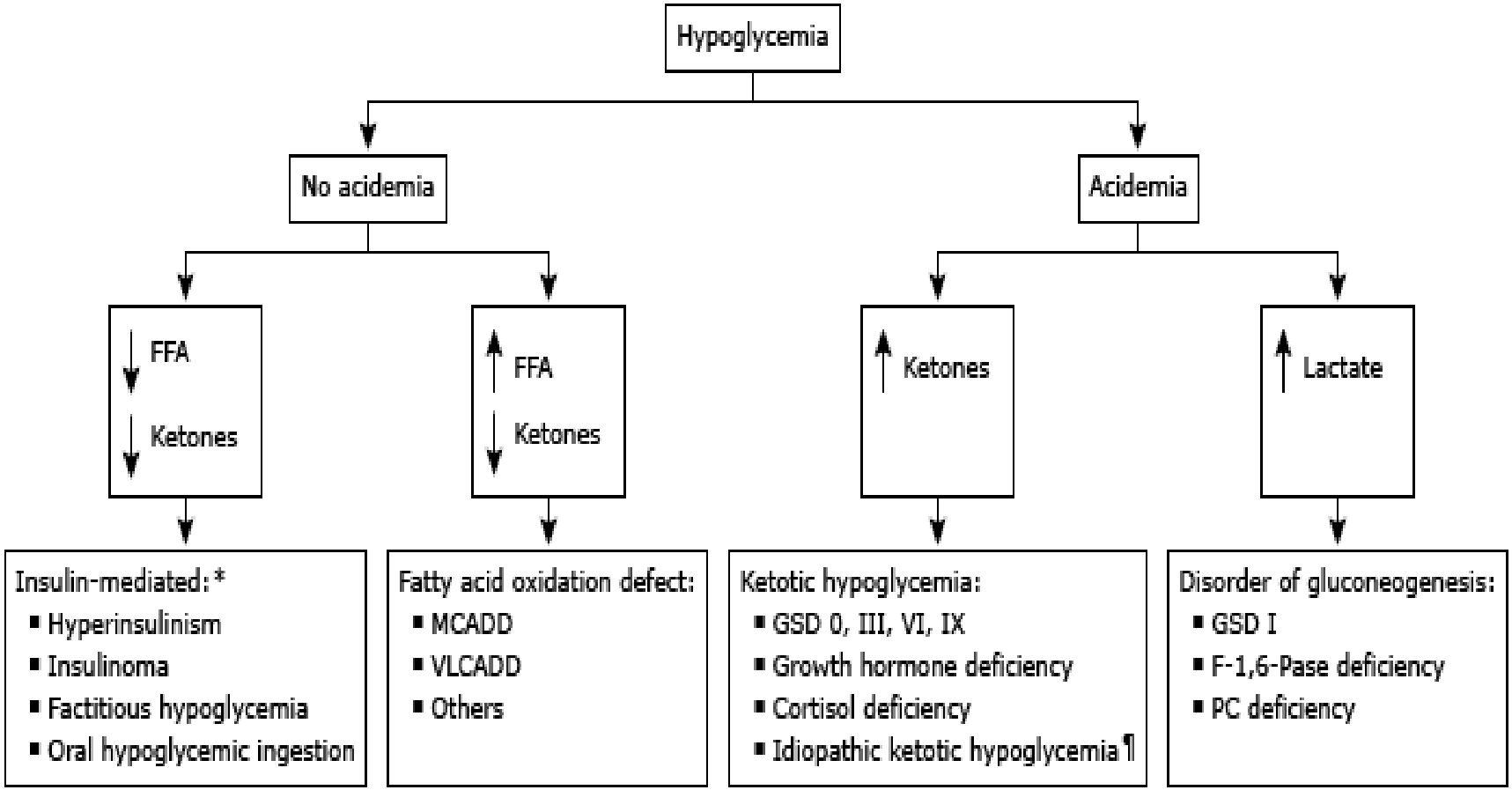
- After the newborn period, patients with deficiencies of cortisol and growth hormone can present with ketotic hypoglycemia

Hormone deficiencies

- A brain MRI should also be obtained if the diagnosis of GHD or hypopituitarism is made

Elevated lactate with acidemia

- Elevated lactate levels with acidemia during an episode of hypoglycemia suggest a disorder of gluconeogenesis
- These findings should prompt further testing for the specific disorder, such as GSD I


Hypoglycemia
No acidemia
Acidemia
FFA
Ketones
FFA
Ketones
Ketones
Lactate
Insulin-mediated:*
Hyperinsulinism
Insulinoma
Factitious hypoglycemia
Oral hypoglycemic ingestion
Fatty acid oxidation defect:
MCADD
VLCADD
Others
Ketotic hypoglycemia:
GSD 0, III, VI, IX
Growth hormone deficiency
Cortisol deficiency
Idiopathic ketotic hypoglycemia¶
Disorder of gluconeogenesis:
GSD I
F-1,6-Pase deficiency
PC deficiency

Case 1

- BS=20 mg/dl
- Insulin=28 mIU/ml (up to 29.1)
- C-peptide=3 ng/ml(0.8-4.2)
- Cortisol=19 microgr/dl
- Urine ketone : negative

- شیرخوار 4 ماهه ای به دلیل تشنج بستری شده است .قند خون بیمار در بدو ورود 20mg/dlمی باشد.
- وزن تولد 3.8 کیلوگرم و وزن فعلی 7.5 کیلوگرم می باشد.

Case 2

- BS: 42 mg/dl
- Insulin : 1 mIU/ml
- Cortisol=18 microgr/dl
- Urine ketone:+++
- No acidosis

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وزن کودک 14 کیلوگرم می باشد .


Thanks for your attention