Cases: Inborn Errors of Metabolism

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Case 1:

- 3 day old male brought to the ED for progressive poor feeding, lethargy – admission requested for “rule out sepsis”
- On your assessment, HR 180, RR 90, SaO2 97% RA, BP 80/50, T 36.5. Lethargic and hypotonic
Case 1:

- CBC, lytes, liver enzymes normal
- Cultures all pending
- U/A normal, no ketones
- Gas 7.5/28/24
- Ammonia 400
- BUN 0.8, creatinine 90
Hyperammonemia

- IEM
  - Urea cycle defects
  - Organic acidemias
  - FAODs
  - Galactosemia
  - Hereditary fructose intolerance
  - Hyperornithinemia, hyperammonemia, homocitrullinemia syndrome
  - Pyruvate carboxylase deficiency
  - Hyperammonemia/Hyperinsulinemia syndrome
  - Hereditary fructose intolerance

- Liver
  - Liver failure (any cause)
  - Sepsis
  - Perinatal depression/hypoxia

- Iatrogenic
  - VPA
  - TPN

- Other
  - Transient hyperammonemia of the newborn
  - Transient neonatal hyperammonemia
Work up

- Plasma ammonia level
- Liver function and liver enzymes
- Plasma amino acid
- Urine organic acid
- Lactate levels
- Blood gas
- BUN level
Case 1:

- CBC, lytes, liver enzymes normal
- Cultures all pending
- U/A normal, + ketones
- Gas 7.2/20/10
- Ammonia 400
- BUN 10, creatinine 90
Approach to Hyperammonemia

- **Hyperammonemia**
  - Ensure proper sampling
  - Blood gas
    - Metabolic acidosis
      - Ketones
        - +++Ketones
          - Organic acidemia
        - No Ketones
          - FAOD
            - Reye Syndrome
      - +Ketones
        - FAOD
          - Reye Syndrome
    - Respiratory alkalosis
      - Liver enzymes
        - Liver function test
          - Abnormal
            - Urea/creatinine
              - No/low urea
                - Urea cycle defect
              - High/N urea
                - THAN
          - Abnormal
Case 2

- 3 month male with progressively poor feeding, lethargy, hypoglycemic seizure – admission requested for “rule out sepsis”
- On your assessment, HR 150, RR 48, SaO2 99% RA, BP 80/50, T 36.5.
- Admitted for Abx, but ongoing hypoglycemic every time you try to wean fluids
Glucose Regulation

Eat \[ \uparrow \text{Glucose} \]

\[ \uparrow \text{Insulin} \]

\[ + \text{Glycogenolysis} \]
\[ + \text{Gluconeogenesis} \]
\[ + \text{Lipolysis} \]
\[ + \text{Ketogenesis} \]
\[ - \text{Glucose Uptake} \]

\[ \uparrow \text{Glucagon} \]
\[ \uparrow \text{Growth Hormone} \]
\[ \uparrow \text{Cortisol} \]
\[ \uparrow \text{Epinephrine} \]

\[ \downarrow \text{Glucose} \]

\[ + \text{Glucose uptake in periphery} \]
\[ + \text{Glycogen synthesis} \]
\[ - \text{Lipolysis} \]
\[ - \text{Gluconeogenesis} \]
Hypoglycemia

↓ Substrate
- Prolonged fast
- Prematurity
- SGA
- Ketotic Hypoglycemia

Hyperinsulinism
- IDM
- Birth Asphyxia
- Persistent Hyperinsulinemia
- Hypoglycemia of infancy
- Insulin adenoma
- Beckwith Weidman

Decreased Counterregulation
- Panhypopituitarism
- GH deficiency
- ACTH deficiency
- Hypothyroid
- Adrenal insufficiency

Endocrine

Metabolic

Carbohydrate
- Glycogen Storage Diseases (some types)
- Inability to metabolize substrate (fructosemia, galactosemia)
- Gluconeogenesis problem
- Pyruvate metabolism problem

Lipids
- FAOD
- Carnitine Deficiency

Proteins/Amino acids
- Organic Acidemia (PA, MMA, IVA)
- Urea Cycle Defects
- Aminoacidopathy (MSUD)

↑ Demand

Systemic Disorders
- Sepsis
- CHF
- Renal
- Malnutrition
- Shock
- LGA infants?

Drugs
- Insulin
- Sulfonylurea drugs

Liver Failure
Glucose → Glucose 6 Phosphate → Pyruvate

Glycogen → Glycogenolysis → Glucose 6 Phosphate

Galactose → Fructose

Uric Acid → Lactate → Fatty Acids → Triglyceride

Kreb Cycle

Electron Transport Chain
Investigations

The Critical Sample

- Glucose ↓
- Insulin ↓
- Growth Hormone ↑
- Epinephrine ↑
- IGF-1 ↑
- Lactate N
- Pyruvate N
- Blood Gas 7.35/45/24

- Ketones – Urine, serum
- β-hydroxybutyrate ↑
- Free Fatty acids ↑
- Free Carnitine N
- Acyl Carnitine profile N
- Ammonia N
- Urine organic acids P
- Urine amino acids P
- Plasma amino acids P
Investigations
The Critical Sample

- Glucose ↓
- Insulin ↓
- Growth Hormone ↑
- Epinephrine ↑
- IGF-1 ↑
- Lactate ↑
- Pyruvate ↑
- Blood Gas \(7.20/30/60/15\)

- Ketones – Urine, serum
  \(\beta\)hydroxybutyrate ↑
- Free Fatty acids ↑
- Free Carnitine \(\text{N}\)
- Acyl Carnitine profile \(\text{N}\)
- Ammonia \(\text{N}\)
- Urine organic acids \(\text{P}\)
- Urine amino acids \(\text{P}\)
- Plasma amino acids \(\text{P}\)
Investigations

The Critical Sample

- Glucose ↓
- Insulin ↑
- Growth Hormone ↑
- Epinephrine ↑
- IGF-1 ↑
- Lactate N
- Pyrurate N
- Blood Gas 7.35/45/24

- Ketones – Urine, serum
- β-hydroxybutyrate Negative
- Free Fatty acids ↓
- Free Carnitine N
- Acyl Carnitine profile P
- Ammonia P
- Urine organic acids P
- Urine amino acids P
- Plasma amino acids P
Investigations

The Critical Sample

- Glucose ↓
- Insulin ↓
- Growth Hormone ↑
- Epinephrine ↑
- IGF-1 ↑
- Lactate N
- Pyrurate N
- Blood Gas **7.35/45/24**
- Ketones – Urine, serum βhydroxybutyrate **Negative**
- Free Fatty acids ↑
- Free Carnitine N
- Acyl Carnitine profile P
- Ammonia **200**
- Urine organic acids P
- Urine amino acids P
- Plasma amino acids P
Interpretation of The Critical Sample

Hypoglycemia
<2.6 Neonates
<4.0 Child

Critical Sample

Endocrine

↓Ketones
↑Insulin

Hyperinsulinism

Defective Counterregulation

↑Ketones
↓Glucagon, Epinephrine, Cortisol, IGF-1

Metabolic

Ketones

↑Ketones

Ammonia/Gas lactate/pyruvate

Carbohydrate Metabolism Defect

Ammonia/Gas Serum aa, urine aa/oa

Protein Metabolism Defect

↓Ketones
↑FFA

FAOD
Carnitine deficiency

↓Ketones
↑FFA
Resources


- Gregory M. Rice, Robert D. Steiner. Inborn Errors of Metabolism (Metabolic Disorders). *Pediatrics in Review*. January 2016, VOLUME 37 / ISSUE 1

- https://newenglandconsortium.org/

- Gene reviews
Questions

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