Biochemical Profile of a critically ill neonate

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Neonatal Physiology

1. Renal functions

- ↓GFR
- Unable to concentrate urine
- Unable to respond to fluid overload
- ↓ fractional re-absorption of filtered HCO_3,PO_4,amino acids & glucose
- ↓ Urea, ↑ creatinine

2. Water & Electrolytes

- ↑ insensible water loss / prone to dehydration
- Has difficulty in coping with excesses / deficit of salt & water
- In prematures, FENa 1-5% (a salt losing state)
- Hyperkalemia due to anoxia at birth

Neonatal Physiology (cont'd)

3. Acid base balance

- Mild metabolic acidosis (pH 7.30-7.46)-- ↓HCO3 reabsorption / ↓H ion excretion

4. Calcium / P04/ Mg Metabolism

- ↓Ca (1.75-2.0mmol/L) over first 2-3 days, usually asymptomatic
- Symptomatic hypocalcaemia in premature neonates
- ↑PO4 due to ↓GFR and ↑renal tubular reabsorption
- Slightly lower Mg levels at birth

5. Bilirubin Metabolism

- Physiological hyperbilirubinemia, (<200µmol/L, unconjugated) due to ↑cell breakdown, ↓hepatic uptake, defective hepatic conjugation, ↑enteric reabsorption
- Return to normal values (<20µmol/L)in 7-10 days)

Neonatal Physiology (cont'd)

6. Glucose Metabolism

- Tolerate fasting poorly due to low glycogen stores and blunted glycogenolysis / gluconeogenesis
- Relatively large size of brain also contributory

7. Enzymes

- Plasma activity of most enzymes higher than adults e.g. ALT, AST, AP

8. Proteins

- ↓ total protein (45-65g) due to ↓α and β globulins
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9. Ammonia

- Transient neonatal hyperammoniaemia

Challenges at birth

- Prematurity
- Adapting to new external environment
- Inherited metabolic disorders

Inherited metabolic disorders

- Disorders with acute clinical presentation like reluctance to feed, vomiting, abnormal breathing, hypotonia, fits, multiple organ failure, coma and death. A few can be detected by neonatal screening programmes e.g. hypothyroism, galactosemia, PKU

- Disorders with chronic and progressive course like failure to thrive, progressive hepatomegaly or neurological deterioration developing over months or years

Inherited metabolic disorders

Disorders with acute clinical presentation

- Amino acid disorders e.g. Tyrisonemia type1, maple syrup urine disease, non ketotic hyperglycinaemia
- Carbohydrate disorders e.g. Galactosemia, glycogen storage diseases type 1(von Gierk's disease)
- Organic acid disorders e.g.isovaleric acidemia, propionic acidemia

Inherited metabolic disorders

- Urea cycle defects e.g. argininosuccinic aciduria, citrullinaemia, ornithine transcarbymylase deiciency
- Steroid synthesis defect e.g. Congenital adrenal hyperplasia

Inherited metabolic disorders

The index case

1. Initial testing

- Plasma: ABgs, electolytes, anion gap, glucose, LFTs, Ca, Mg
- Urine: Glucose, ketones, reducing substances, pH

Inherited metabolic disorders

2. Follow up investigations

- Hypoglycemia:

  Consider glycogen storage disease, disorders of gluconeogenesis, amino acid disorders and organic acidaemias

Plasma: lactate, insulin, cortisol

Urine: amino acids, organic acids

Inherited metabolic disorders

- Metabolic acidosis (High anion gap):

  Consider organic acidemias, congenital lactic acidosis

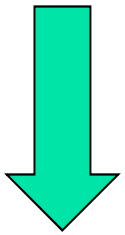
Plasma: lactate, ammonia

Urine: amino acids, organic acids

Inherited metabolic disorders

Respiratory alkalosis:

Consider urea cycle defects



Plasma ammonia

urine amino acids

Inherited metabolic disorders

Abnormal liver function tests

Consider galactosemia, fructose intolerance, tyrosinemia, glycogen storage disease, disorders of gluconeogenesis

Plasma lactate, α1-antitrypsin

urine sugars, ketones, amino acids, organic acids

Neonatal hyperbilirubinaemia

Aetiology

1. Predominantly Unconjugated hyperbilirubinaemia

- Physiological
- Breast milk jaundice
- Haemolytic anaemia
- Hypothyroidism
- Inborn errors of metabolism: Gilbert's disease, Criggler - Najjar syndrome

Neonatal hyperbilirubinaemia

2. Predominantly conjugated hyperbilirubinaemia

- Inborn errors of metabolism: Dubin-Johnson syndrome, Rotor syndrome
- Neonatal hepatitis: CMV, rubella, Hep B
- Alpha 1 antitrypsin deficiency
- Lipoidosis:Niemann- Pick disease,Gaucher's disease
- Cystic fibrosis
- Hypothyroidism
- Biliary atresia

Neonatal hyperbilirubinaemia

Other biochemical tests

1. Serum LDH/Haptoglobin: ↑ in hemolytic jaundice
2. Plasma Transaminases: In hepatocellular diseases levels >10 times URL
3. Plasma AP / Gamma GT / 5-nucleotidase: Levels >5 times URL in obstructive jaundice
4. Alpha 1 antitrypsin : ↓or absent in Alpha 1 antitrypsin deficiency
5. Serum TSH: ↑ TSH in congenital hypothyroidism
5. Urinary sugars: galactose in galactosemia, fructose in hereditary fructose intolerance
6. Sweat electrolytes: Sweat Na/Cl >60mmol/L in cystic fibrosis

Neonatal hypoglycemia

Etiology

1. Transient: small for dates, sepsis/asphyxia/cerebral hemorrhage, diabetic mother

2. Persistent: organic acidurias,hormone deficiencies e.g. GH, thyroxine, nesidioblastosis

Neonatal hypoglycemia

Biochemical tests

1. Plasma glucose: <2.2 mmol/L
2. Plasma Lactate: ↑ in defects of gluconeogenic pathway
3. Plasma FFAs: ↑ levels indicate lipolysis associated with ketotic hypoglycemia / disorders of fatty acid oxidation
4. Plasma alanine: ↓ levels in ketotic hypoglycemia
5. Plasma ammonia: ↑ in some organic aciduria
6. Urinary ketones: indicate lipolysis, ↑in hypoinsulin disorders e.g. small for dates baby, not detected in hyperinsulinemic disorders e.g. in neonates of diabetic mother
7. Reducing sugars: e.g.galactose in galactosemia

Neonatal hypoglycemia

8. Enzyme defects:
   - Carbohydrates: glycogen synthase, glucose 6 phosphatase
   - Amino acids: Branched chain keto acid dehydrogenase
   - Fatty acids: carnitine palmatyl transferase
   - Organic acidurias: Propionic / methlmalonic aciduria
9. Hormone studies: Gh deficiency, hypothyroidism

Neonatal hyperammonemia

Etiology

1. Urea cycle defects: e.g. carbamoyl phosphate synthase deiciency
2. Organic acidurias: e.g. propionic aciduria
3. Disorders of fatty acid metabolism: e.g. deficiency of hydroxymethylglutaryl-CoA
4. Liver disorders: e.g. Reye's syndrome
5. Transient neonatal hyperammonemia

Neonatal hyperammonemia

Biochemical tests

1. Plasma anion gap: ↑ in organic acidurias
2. LFTs: ↑ aminotransferases
3. Plasma aminoacids: glutamine, citrulline, arginine
4. Urinary organic acids: arginosuccinic acid, orotic acid
5. Enzyme analysis: urea cycle enzymes in liver tissues

Electrolyte abnormalities

1. Hypernatremia: plasma Na > 150mmol/L, implies water deficit relative to body solute content
   - Causes: pure water depletion, vomiting dirrhoea, mineralocorticoid deficiency, inappropriate i/v therapy
2. Hyponatremia: plasma Na < 130mmol/L, implies extracellular water excess relative to body solute content
   - Causes: inappropriate i/v therapy
3. Hypokalemia: plasma K <3.5 mmol/L
   - Causes: vomiting dirrhoea, mineralocorticoid excess, inappropriate i/v therapy
4. Hyperkalemia: plasma K > 5.8 mmol/L
   - Causes: pseudohyperkalemia, inappropriate i/v therapy

Calcium abnormalities

1. Hypocalcemia:

- Causes: transient neonatal hypocalcemia (early / late), hypoparathyroidism (rare,part of DiGeorge syndrome), pseudo hypoparathyroidism (end organ resistance), magnesium deficiency, inappropriate i/v therapy

2. Hypercalcemia:

- Cause: Primary HPT (rare)

Conclusion

Biochemical tests in neonates provide important investigative tool in diagnosing a variety of disorders without which many diseases particularly inborn errors of metabolism will remain an enigma. It is important to rationalize these investigations in clinical perspective in order to save time and lab resources