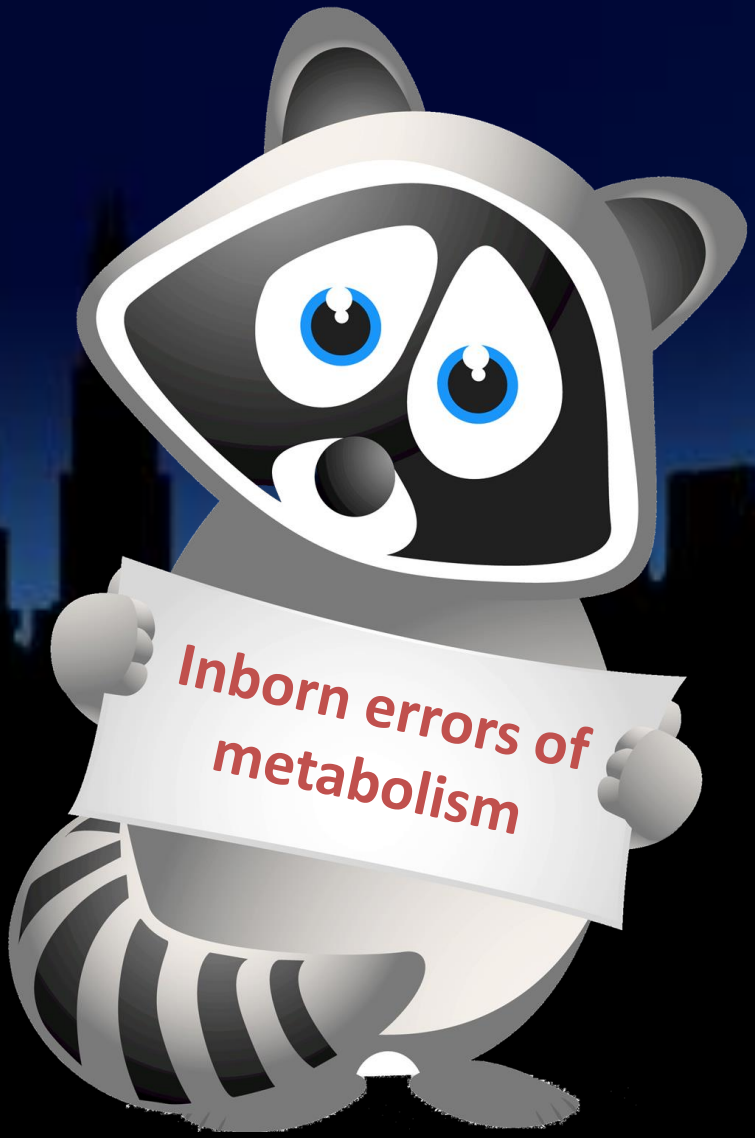
The McMaster *at night* Pediatric Curriculum



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(faculty review by Dr. M. Kozenko)

Inborn errors of metabolism, Pediatrics in review
Rice et all

Objectives – Medical expert

1. Have an organized framework for metabolic disorders
2. Understand the main differences between the different types of metabolic disorders
3. Recognize metabolic emergencies such as hyperammonemia and know how to manage it
4. Develop a broad differential diagnosis for metabolic conditions

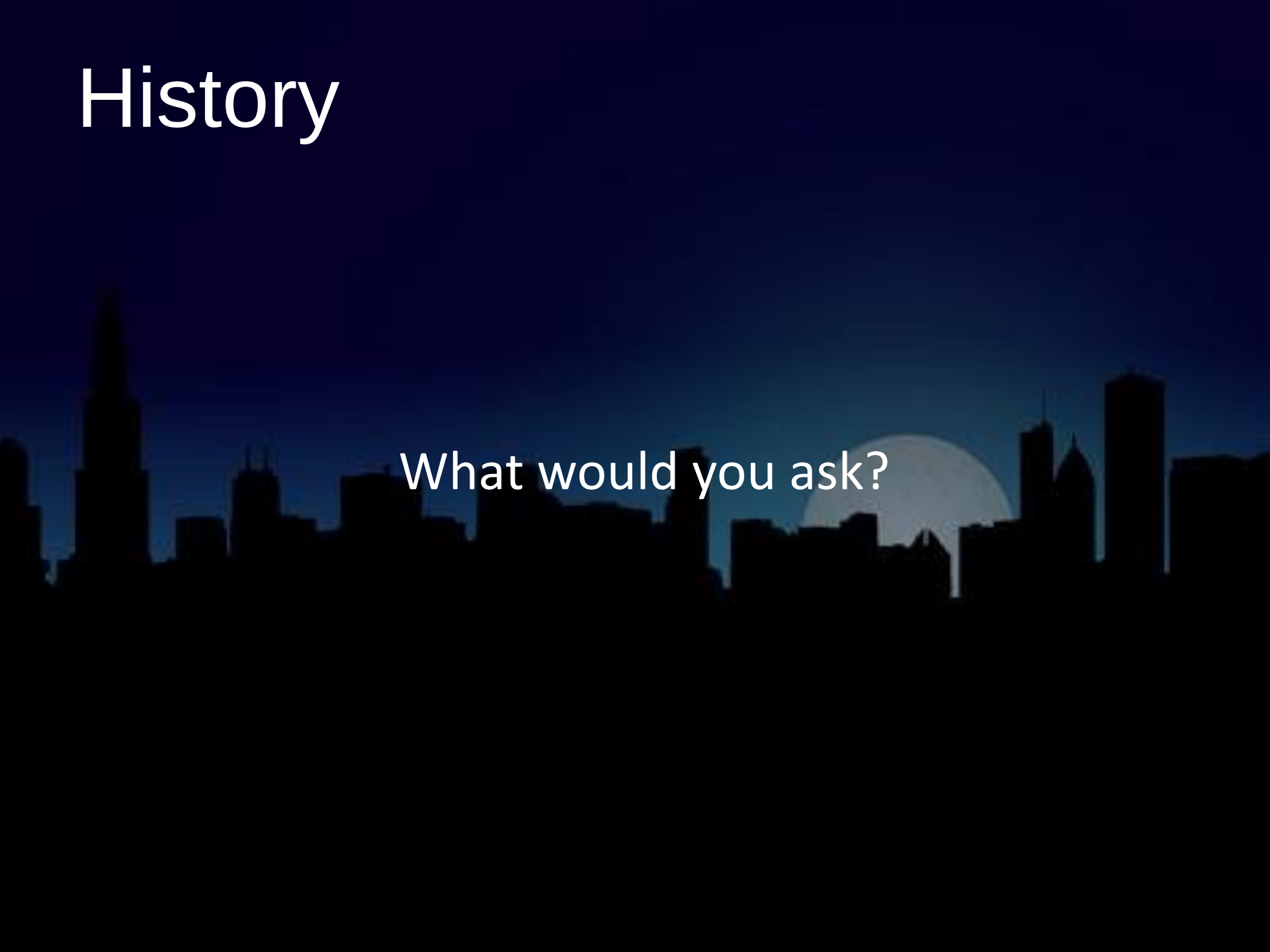
Background

- Metabolic disorders are difficult to master
- Many metabolic disorders have similar clinical presentations
- Classified according to the defect in the metabolism of energy sources: lipids, proteins, carbohydrates
- Protein: aminoacidopathies, organic acidemias, urea cycle disorders
- Lipids: defects in fatty b-oxidation
- Carbohydrate: galactosemia, glycogen storage disorders
- Lysosomal: inability to digest or recycle large complex macromolecules

The Case

- 6 days old baby seen in the ER after ”turning blue” at home
- Mother noticed he was cyanotic and stopped breathing
- Mom described his arms as getting “rigid” but no other abnormal movements
- Prior to this the baby had been doing well at home

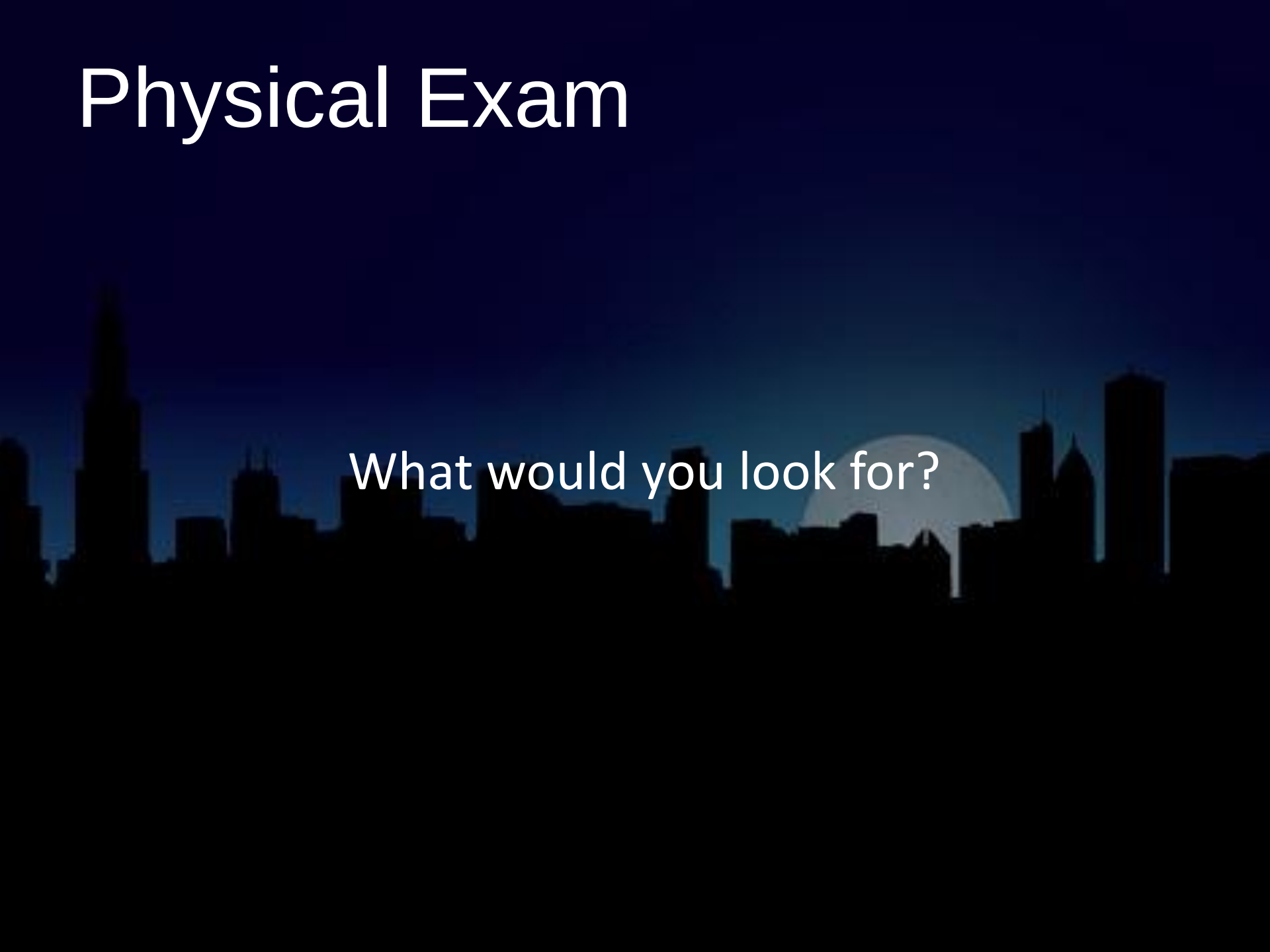
History



History

- Antenatal history
- Birth history: gestational age, APGARS, resuscitation, neonatal issues
- State during the event: awake or asleep, position: supine, prone; feeding? Abnormal color? Abnormal breathing? Seizures?
- Previous episodes of BRUE (brief resolved unresponsive event)
- Breathing problems, cyanosis
- Sweating with feeds, respiratory distress
- Vomiting, signs of GERD
- History of seizures
- Previous hospitalizations
- Feeding history
- Social hx: keep a high suspicion for child abuse if nothing fits with the history
- Family hx: consanguinity, metabolic disorders, neonatal deaths

Physical Exam



What would you look for?

Physical Exam

- General appearance: alert, drowsy, unconscious
- Height, weight, head circumference
- Vital signs
- Skin: color, perfusion
- Head: anterior fontanelle, dysmorphic features
- Eyes: retinal exam, extraocular movements
- Chest: inspection of chest, auscultation for adventitious sounds, look for signs of respiratory distress
- CVS: central and peripheral pulses, 4 limb blood pressure, pre and post ductal oxygen saturations, rhythm, abnormal heart sounds
- Abdomen: masses, organomegaly
- Genitalia: look for abnormalities such as microphalus, clitoromegaly
- Neuro: primitive reflexes, central and peripheral tone

Workup

Basic laboratory investigations

1. Electrolyte
2. Blood Gases
3. Blood glucose
4. Ammonia
5. Urine ketones
6. Lactate

Specific Workup

1. Plasma amino acids
2. Urine organic acids
3. Acylcarnitine profile
4. Review a result from newborn screening

	Fatty acid oxidation defects	Organic acidemias	Aminoacidopathies	Urea cycle disorders
Metabolism	Defect in beta oxidation of fatty acids	Defect in amino acid breakdown leads to accumulation of organic acid byproducts	Defect in amino acid breakdown leads to accumulation of intact amino acids	Defect in making urea from ammonia that results from amino acid breakdown
Disorder	Medium chain acyl CoA dehydrogenaselong chain 3 hydroxy acyl CoA dehydrogenase very long chain acyl CoA dehydrogenase	Propionic Methylmalonic Isovaleric	Maple syrup urine Phenylketonuria Homocystinuria Tyrosinemia	Ornithine transcarbamylase (x-linked) Citrulinemoa Arginosuccinic aciduria
Presentation	Hypoketotic hypoglycemia lethargy, vomiting, sudden infant death Long chain disorders: cardiomyopathy and rhabdomyolysis	Metabolic acidosis with anion gap Neonatal lethargy, vomiting, coma, strokes, death	No acidosis or hyperammonemia	Hyperammonemia without acidosis Neonatal lethargy, vomiting, coma, death
Investigations	NBS Plasma acylcarnitines No or inappropriately low ketones	NBS Urine organic acids Plasma acylcarnitines	NBS Plasma amino acids	NBS Hyperammonemia Plasma aminoacids Urine orotic acid
Acute treatment	10 % dextrose with NS	10% dextrose with NS Early use of fluids No protein IV lipid emulsion Dyalisis in sick neonates	Similar to organic acidemias Avoid hyponatremia	10% dextrose with salt Early use of fluids Sodium benzoate/phenylacetate Arginine dyalisis
Chronic management	Low fat diet, avoid prolonged fasting, nighttime feeds when sick, carnitine, echo for long chain fatty acid oxidation disorders	Low protein diet Supplemental medical food Carnitine Liver transplantation	Restrict offending amino acid Supplemental food Monitor plasma amino acids	Low protein diet Supplemental food Phenylbutyrate Arginine/citrulline Liver transplantation

Differential Diagnosis

Here	
CNS	Seizures
Cardiovascular	Congenital cardiac defects, arrhytmias
Respiratory	Choanal atresia, TEF, upper/lower airway obstruction
GI	GERD
ID	Sepsis
Metabolic	Inborn errors of metabolism
Neurometabolic conditions	
Endocrine	Hypoglycemia, CAH
Hematology	anemia
Social	Child abuse

Protein disorders : Aminoacidopathies, Organic acidemias and Urea cycle disorders

- Aminoacidopathies → autosomal recessive

- Phenylketonuria:
- - deficiency of pehnylalanine hydroxylase (PAH) → hydroxylates phenylananine (phe) to tyrosine. Phe and phenylketones silently accumulate and cause brain injury (microcephaly, developmental delay)
  - Maternal PKU syndrome → dysmporphic features, microcephaly, IUGR and congenital heart disease
  - Treatment → lifelong restriction of Phe via dietary protein restriction and supplementation with phe-free medical foods/beverages to prevent protein deficiency

Aminoacidopathies

Maple syrup urine disease

-Deficiency in alpha-ketoacid dehydrogenase which aids in the metabolism of branched-chain amino acids (isoleucine, valine and leucine)

- Most common among older order Mennonites
- Diagnosis: elevated branched chain amino acids on PAA and UOA
- Presents during the first week with lethargy, poor feeding → if not recognized and treated → hypertonia, coma and death
- Acute metabolic decompensation due to neurotoxic effects of leucine
- Older children: headache, confusion, hallucinations, lethargy and vomiting

- Management: stop leucine intake (protein intake), administer high dextrose content isotonic IV fluids, BCAA-free parenteral nutrition
- Never hypotonic fluids → risk of cerebral edema
- Dialysis → emergency treatment for the hyperammonemia
- Long-term → liver transplant can help preventing acute decompensations

Aminoacidopathies

- Homocystinuria:
- - Deficiency in cystathionine beta-synthetase
- Diagnosis: elevated Homocysteine

- No acute metabolic decompensations but results in intellectual disability
- PE: tall stature, risk for stroke, osteoporosis, recurrent thrombosis and ectopia lentis
- Differential dx for Marfan syndrome
- Treatment: Vitamin B6, Vitamin B12, betaine and diet
- Dietary methionine restriction

Aminoacidopathies

- Tyrosinemia:
- Type I: defect in fumarylacetoacetate
- Confirmation of diagnosis by urine organic acids (elevated succinylacetone) and PAA (elevated tyrosine and methionine)
- When untreated → liver failure in infancy or early childhood
- RTA and recurrent episodes of neuropathic pain can occur
- Treatment → nitisinone(NTBC) and tyrosine restriction
- Long term → liver transplant

Aminoacidopathies

- Non- ketotic hyperglycinemia
  - Lethal deficiency in glycine cleavage, results in elevated glycine levels in CSF → leads to seizures, hiccups and apnea in the neonatal period

Organic acidemias

- Organic acids are the deaminated remains of AA
- Inheritance: AR
- Defects in degradation result in massive accumulation in blood and urine leading to metabolic acidosis with elevated anion gap
- Infants → poor feeding, tachypnea, vomiting lethargy
- NBS → elevated acylcarnitines (C3, C5)
- Diagnosis → UOA and acylcarnitine profile
- Treatment → stop protein, administer high doses of carnitine supplements and promote anabolic state with dextrose containing fluids (10% dextrose in NS), IV lipid emulsions and insulin
- IV bicarbonate to correct acidosis
- Hemodyalisis → for hyperammonemia

Organic acidemias

- Propionic acidemia:

- Caused by propionyl CoA carbolxylase defect → leads to to abnormal metabolism of isoleucine, valine, methionine and threonine
- UOA → elevated 3-OH propionic acid and methylcitrate
- NBS shows elevated C3 acylcarnitine and PAA elevated glycine
- Newborns: overwhelming metabolic acidosis with high anion gap, prominent ketosis
- Metabolic acidosis, Hyperammonemia
- Brain injury leads to permanent intellectual disability or movement disorders
- Elevated urine ketones are an early sign of metabolic crisis
- Liver transplantation may decrease the frequency of metabolic crisis
- Late onset cardiomyopathy and arrhythmias

Organic acidemias

- Methylmalonic acidemia
- Deficiency in methylmalonic CoA mutase
- Can also happen due to defects in cobalamin metabolism
- Presents in the newborn period similar to propionic acidemia = acidosis, ketosis and hyperammonemia
- UOA → elevated methylmalonic acid and methylcitrate
- PAA → elevated C3 acylcarnitine, alanine and glycine
- Metabolic crisis → stroke, intellectual disability and movement disorder
- Treatment → dietary restriction of offending amino acid, vitamin B12 and carnitine

Organic acidemias

- Glutaric acidemia:
- Type 1 → defect in glutaryl CoA dehydrogenase → metabolism of acids tryptophan and lysine
- More common in Amish individuals
- Severe cerebral organic acidemia
- Metabolic acidosis, ketosis and hyperammonemia not present during an acute episode
- Permanent injury of basal ganglia → movement disorders following a fever associated with a mild illness → treat agresively with dextrose containing fluids
- NBS: elevated C5
- Diagnosis: elevated uribe gkutaric and 3-OH glutaric acid on UOA analysis and C5DC acylcarnitine elevated on plasma and urine acylcarnitine analysis
- Children often present with macrocephaly, dystonia, movement disorders, subdural hematomas
- Treatment → carnitine supplementationand dietary lysine and tryptophan restriction but most important is to avoid catabolism during illness providing glucose containing fluids
- Other OA: isovaleric acidemia

Urea cycle disorders

- Hyperammonemia:
- Urea cycle dysfunction leading to accumulation of ammonia in the blood
- Presentation: altered mental status, lethargy, vomiting, cerebral edema, coma and death
- Hyperammonemic encephalopathy is a medical emergency
- Severe metabolic acidosis is not a feature
- Recurrent, unrecognized episodes can lead to global developmental delay, spasticity and intellectual disability
- Investigations: Ammonia level, LFTs, electrolytes, UOA and PAA
- Treatment → cessation of protein intake, reduction of catabolic stress (IV D10NS and IV lipid emulsion), central venous access for for delivery of arginine hydrochloride with sodium phenylacetate and sodium benzoate
- Avoid hyponatremia given the risk of cerebral edema
- Dialysis for severe hyperammonemia
- Long-term management: dietary protein restriction, arginine or citrulline supplementation, sodium phenylbutyrate or sodium phenylacetate.
- Liver transplantation reduces the episodes of recurrent hyperammonemia

Urea cycle disorders

- OTC deficiency:
- X-linked
- Recurrent episodes of hyerammonemia associated with catabolic stress or excessive protein intake
- Elevated plasma ammonia, elevated glutamine on PAA with decreased citrulline and arginine
- UOA in affected males: elevated orotic acid
- Longterm: citrulline supplementation, dietary protein restriction, oral sodium or glycerol phenylbutyrate
- Liver transplant for recurrent episodes of hyperammonemia

Lipid metabolism(fatty oxidation)

- FAOD:
- Defect in beta oxidation of fatty acids or carnitine metabolism
- Autosomal Recessive
- Patients can not metabolize fatty acids --> cannot release stored energy → leads to hypokethotic hypoglycemia
- Hypoglycemia with intercurrent illness → brain injury, seizures
- Treatment: avoid prolonged fasting, IVD10NS , supplemental carnitine

Fatty acid oxidation

- MCAD deficiency:
- MCAD enzyme breaks down medium chain fatty acids to short chain fatty acids and acetyl CoA which provide energy for gluconeogenesis and ketone body formation
- Prolonged fasting triggers hypoglycemic episodes
- Diagnosis: plasma acylcarnitine profile shows elevated C6,C8 and C10 acylcarnitines
- UOA: elevated hexanoylglycine and suberylglycine
- Treatment: avoid fasting during intercurrent illness is the most important intervention + carnitine supplementation

Fatty acid oxidation

- LCHAD/VLCAD
- - very long chain acyl CoA dehydrogenase and long-chain 3 hydroxy acyl CoA dehydrogenase deficiencies
- Can result in rhabdomyolysis, cardiomyopathy, liver dysfunction and recurrent hypoketotic hypoglycemia
- May also result in retinopathy and peripheral neuropathy
- PAC profile: elevated C14 in VLCAD and C16 in LCHAD
- Treatment: fat restriction and supplementation with medium chain triglyceride oil to provide muscles with a usable source of energy
- Avoid fasting to prevent hypoglycemia
- Dextrose containing fluids
- Carnitine supplementation controversial
- CK should be followed up given the risk of rhabdomyolisis

Carbohydrate disorders

- Galactosemia:

- Autosomal Recessive

- Deficiency of galactose I phosphate uridyltransferase → leads to accumulation of galactose and galactose I phopsphate
- Lactose ingestion leads to metabolic decompensation
- Liver dysfunction, jaundice and coagulopathy develop
- If diagnosed late --> learning disability
- Females → ovarian failure requiring estrogen replacement in adolescence
- Diagnosis: GALT level and blood galactose I phosphate values plus DNA
- Chronic management: lifelong dietary restriction of galactose

Glycogen storage disorders

- Inability to degrade stored glycogen in the liver and muscle
- GSDI → fasting hypoglycemia
- GSDIa → deficiency in glucose 6 phosphatase → resuls in massive hepatomegaly, growth failure and recurrent episodes of ketotic hypoglycemia
- Elevated lactic, uric acids and triglycerides
- Frequent cornstarch or continuous gastrostomy feeds needed to prevent recurrent hypoglycemia
- Late complications → hepatic adenomas, hypertension and renal insufficiency
- GSDIb → neutropenia, frequent infections and inflammatory bowel disease
- GSDV → presents in adolescence with exercise induced muscle pain, fatigue and rhabdomyolisis → diagnosis by muscle biopsy and genetics
- Other: hereditary fructose intolerance, glycogen synthase deficiency

Lysosomal storage disorders

- Accumulation of large macromolecules (mucopolysaccharides, sphingolipids, oligosaccharides)
- Progressive involvement of liver, spleen, brain or bones
- Clinical features: hepatosplenomegaly, bone deformity, developmental regression, hearing and vision impairment and coarse facial features
- Most autosomal recessive except Fabry disease and MPS type II (Hunter disease) which are x-linked
- Diagnosis: urine glycosaminoglycan analysis for MPS and urine oligosaccharides, demonstration of the enzymatic defect in lymphocytes or fibroblasts and DNA test

Peroxisomal disorders

- Infantile hypotonia, skeletal dysplasia, hearing and vision loss, hepatomegaly, neurologic regression in childhood
- MRI --> leukodystrophy
- Adrenoleukodystriphy → x linked, deficiency in peroxisomal oxidation of VLCFAs → developmental regression, new onset spasticity and adrenal failure in school age boys
- diagnosis: plasma VLCFA
- HSCT may halt progression in some patients

Mitochondrial disorders

- Transmitted via maternal inheritance(not always)
- Most important mitochondrial function → production of cellular energy
- Results in dysfunction in tissues with the highest energy demands: brain, skeletal, cardiac muscles and the eye
- Muscle biopsy may show ragged fibers on light microscopy
- Diagnosis: DNA sequencing of multigene panels for nuclear genetic mutations, sequencing of the mitochondrial genome and specific assays of muscle respiratory chain activity

Test your knowledge

- You are seeing a 5-day-old newborn in your office for an initial health supervision visit. The mother reports an unremarkable pregnancy and delivery, with a brief period of hypoglycemia after delivery that resolved quickly with the first feeding. The newborn has been feeding well without signs of lethargy since that time. His physical examination is unremarkable. The mother is anxious, having had an infant 10 years ago who died of sudden infant death syndrome after a 2-day respiratory illness while the family was living abroad. You received notification today that this newborn's screening test was flagged for elevations of C6, C8, and C10 acylcarnitines, with the C8 level most significantly elevated. As prescribed in the ACT algorithm published by the American College of Medical Genetics, you order a blood glucose and electrolyte levels, blood gas, liver function tests, urine organic acids, urine acylglycines, and a plasma acylcarnitine profile.
- The laboratory results reveal:
- Plasma acylcarnitine profile: elevated C8
- Urine organic acids: slightly elevated dicarboxylic acids
- Urine acylglycines: elevated hexanoylglycine
- Blood glucose, liver function tests, blood gas, and electrolyte levels were all normal

Answers options:

A. Carnitine palmitoyltransferase-2 deficiency
B. Maple syrup urine disease
C. Medium-chain acyl-coenzyme A dehydrogenase deficiency
D. Phenylketonuria
E. Propionic aciduria

Source: prep questions 2017

The answer…

Answers options:

A. Carnitine palmitoyltransferase-2 deficiency
B. Maple syrup urine disease
C. Medium-chain acyl-coenzyme A dehydrogenase deficiency
D. Phenylketonuria
E. Propionic aciduria

Test your knowledge

- You are called urgently to the newborn nursery to assess a neonate with a change in neurologic status. The female neonate was born at full term after an uncomplicated pregnancy and delivery. Her first 24 hours after birth were symptom-free, after which she developed a poor suck with difficulty feeding. Her condition continued to worsen, progressing to vasomotor instability, lethargy, seizures, and then obtundation on day 4 after birth. Chest radiography, lumbar puncture, and head ultrasonography yielded normal results. Blood, urine, and cerebrospinal fluid cultures are pending. Her C-reactive protein level is normal. A complete blood cell count shows thrombocytopenia and neutropenia. Further laboratory testing reveals a metabolic acidosis with a high anion gap, hyperammonemia, ketonuria, and hypoglycemia. On day 5 after birth, you are notified that her newborn screen has been flagged for an elevated C3 acylcarnitine.
- Of the following, the laboratory test MOST likely to determine this neonate's diagnosis is

Answer options:

A. 17-OHP level
B. Biotinidase level
C. Carnitine profile
D. Lactate level
E. Urine organic acids

Source: prep questions 2017

Answer options:

A. 17-OHP level
B. Biotinidase level
C. Carnitine profile
D. Lactate level
E. Urine organic acids

Summary

- Metabolic disorders are complex
- Keep a high index of suspicion when a baby presents with lethargy
- Approach according to the defect in the metabolism of energy sources: lipids, proteins, carbohydrates
- If hyperammonemia present call METABOLICS right away! Ask for help! METABOLIC EMERGENCY!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