INBORN ERRORS OF METABOLISM, PART 1

Michelle Y. Spencer, MD

University of Florida Neonatal Grand Rounds

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DISCLOSURE STATEMENT

- I have no relevant financial relationships to disclose or conflicts of interest to resolve.

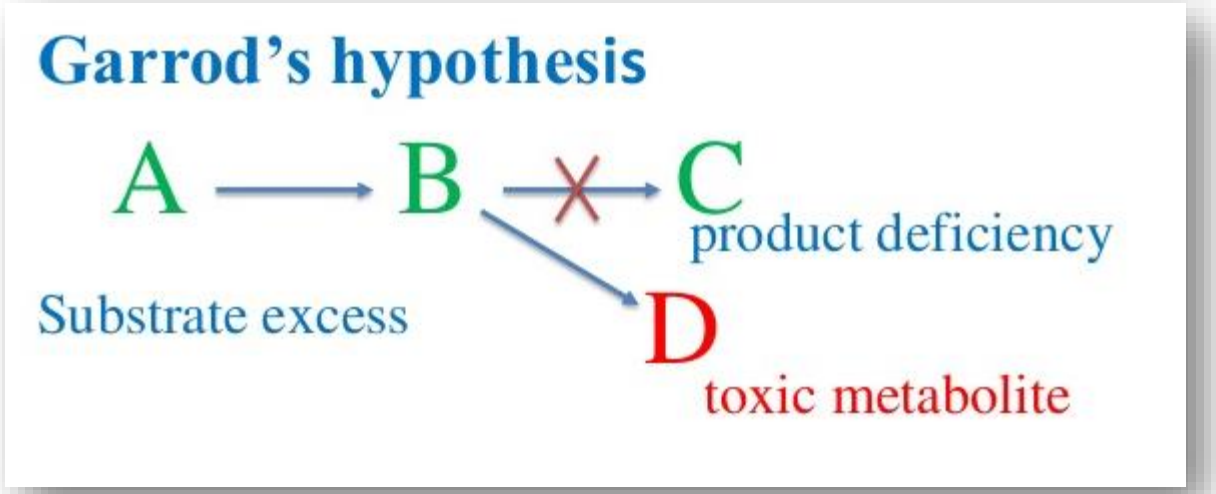
- I will not discuss any unapproved or off-label, experimental or investigational use of a product, drug or device.

LEARNING OBJECTIVES

1. Describe inborn errors of metabolism in neonates
2. Discuss methods for early recognition and treatment of neonates with inborn errors of metabolism
3. Review differential for metabolic encephalopathy in the newborn.
4. Discuss advances in neonatal care of patients with inborn errors of metabolism

INTRODUCTION

- Inborn errors of metabolism are inherited biochemical disorders with specific enzyme defect that interferes with the normal metabolism of protein, fat or carbohydrate.
- Subgroups
  - **Disorders of Protein metabolism**
    - Disorders of Amino Acid Metabolism
    - Urea Cycle Defects
    - Organic Acidemias
  - **Disorders of Carbohydrate Metabolism**
  - Lysosomal Storage Defects
  - Peroxisomal Disorders
  - Endocrine Disorders
  - Fatty Acid Oxidation
  - Mitochondrial Disorders

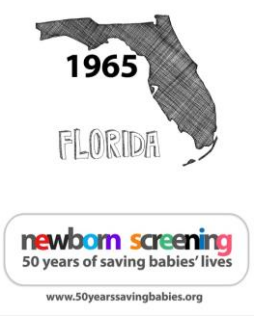


FLORIDA STATE NEWBORN SCREEN

- Newborn Screening was established in 1963
  - Considered the most successful public health initiative in the nation
  - 1 in 300 newborns have a condition detectable by newborn screen
- Florida currently screens for 36 conditions
  - This includes about 20 metabolic disorders
- Blood testing results for metabolic tests are usually ready within 5 days after the sample is collected
- **NOTE:** Parents have the option to **OPT OUT** of newborn screening







newborn screening
50 years of saving babies' lives
www.50yearssavingbabies.org

WHEN TO CONSIDER . . . INBORN ERRORS OF METABOLISM

- Normal infant at birth (usually term)*
- Illness presentation within first 48 hours of age

- FAMILY HISTORY
  - Neonatal death of unclear etiology
  - History of child with neurologic deterioration
  - History of multiple miscarriages
  - Consanguinity

- CLINICAL PRESENTATION
  - Poor oral intake &/or vomiting
  - Lethargy coma, seizures, changes in tone or reflexes
  - Hepatosplenomegaly, dysmorphic features
  - Cataracts

DIFFERENTIAL INCLUDES AN INBORN ERROR OF METABOLISM

Emergent Management

1. Stop all enteral feeds to eliminate protein, galactose and fructose
2. Change IV fluids to D10 to deliver GIR 8-10 mg/kg/min. Discontinue IV lipids
   - Even if insulin is required to maintain blood glucose
3. Treat any significant acidosis (pH <7.22)
4. Eliminate toxic metabolites
   - Ammonia < 500 $\mu M/L$ → Sodium Benzoate OR Phenylacetate
   - Ammonia > 500 $\mu M/L$ → Hemodialysis
5. Consult Genetics

DIFFERENTIAL INCLUDES AN INBORN ERROR OF METABOLISM

Primary Evalaution

Send the following laboratory test…

CBC with differential

(neutropenia or thrombocytopenia

Electrolytes and arterial blood gas (acidosis alkalosis, increased anion gap)

Glucose assess presence or absence of ketones

Plasma ammonia concentration*

Lactate and pyruvate concencentrations with ratio of lactate to pyruvate

Liver function tests

Urine ketones

Check newborn screen, if available

Geneticist will likely recommend:

Secondary evaluation

Plasma amino acid analysis

Urine organic acid analysis

Plasma carnitine and acylcarnitine

Plasma uric acid

CSF amino acid analysis

Peroxisomal function test

INBORN ERRORS OF METABOLISM: LAB FINDINGS

Anion Gap Metabolic Acidosis	
Organic Acidemias	Propionic, Isovaleric and Methylmalonic Acidemia
Fatty Acid Oxidation,	Short, medium long chain abnormalities Carnitine Deficiency
Congenital Lactic Acidosis	Pyruvate Dehydrogenase, Mitochondiral Disorders of Respiratory Chain
Secondary Lactic Acidosis	Hereditary fructose intolerance, **glycogen storage disease type I, organic acidemias**
Other	**Prematurity** (liver failure from TPN), **HIE,** severe hepatitis, abnormal mitochondrial oxidation from hypoxia

Respiratory alkalosis

Urea cycle defects

Normal Anion Gap

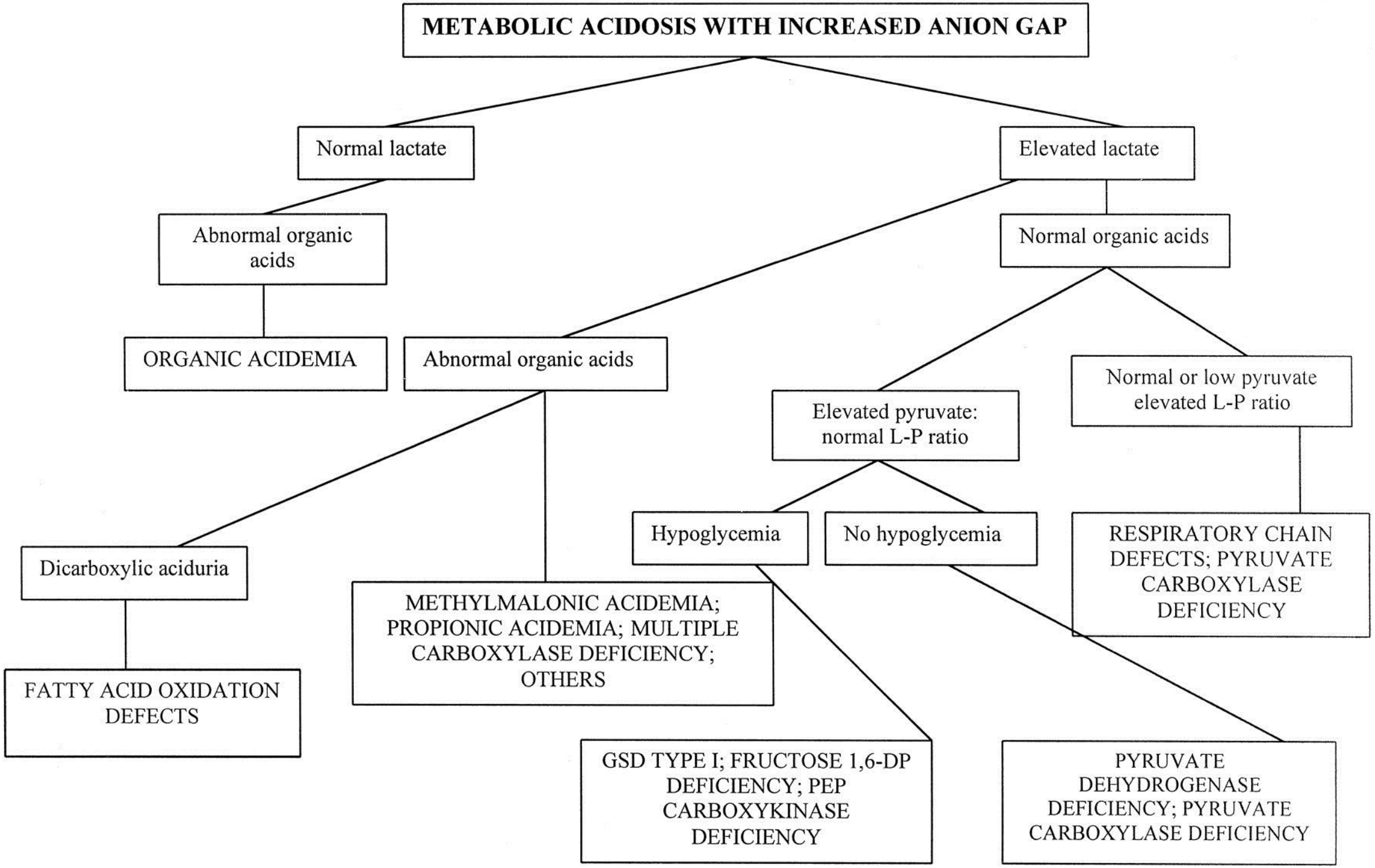
Diarrhea, RTA, **galactosemia, tyrisonemia**, some mitochondrial disorders or respiratory chain

Neutropenia & Thrombocytopenia

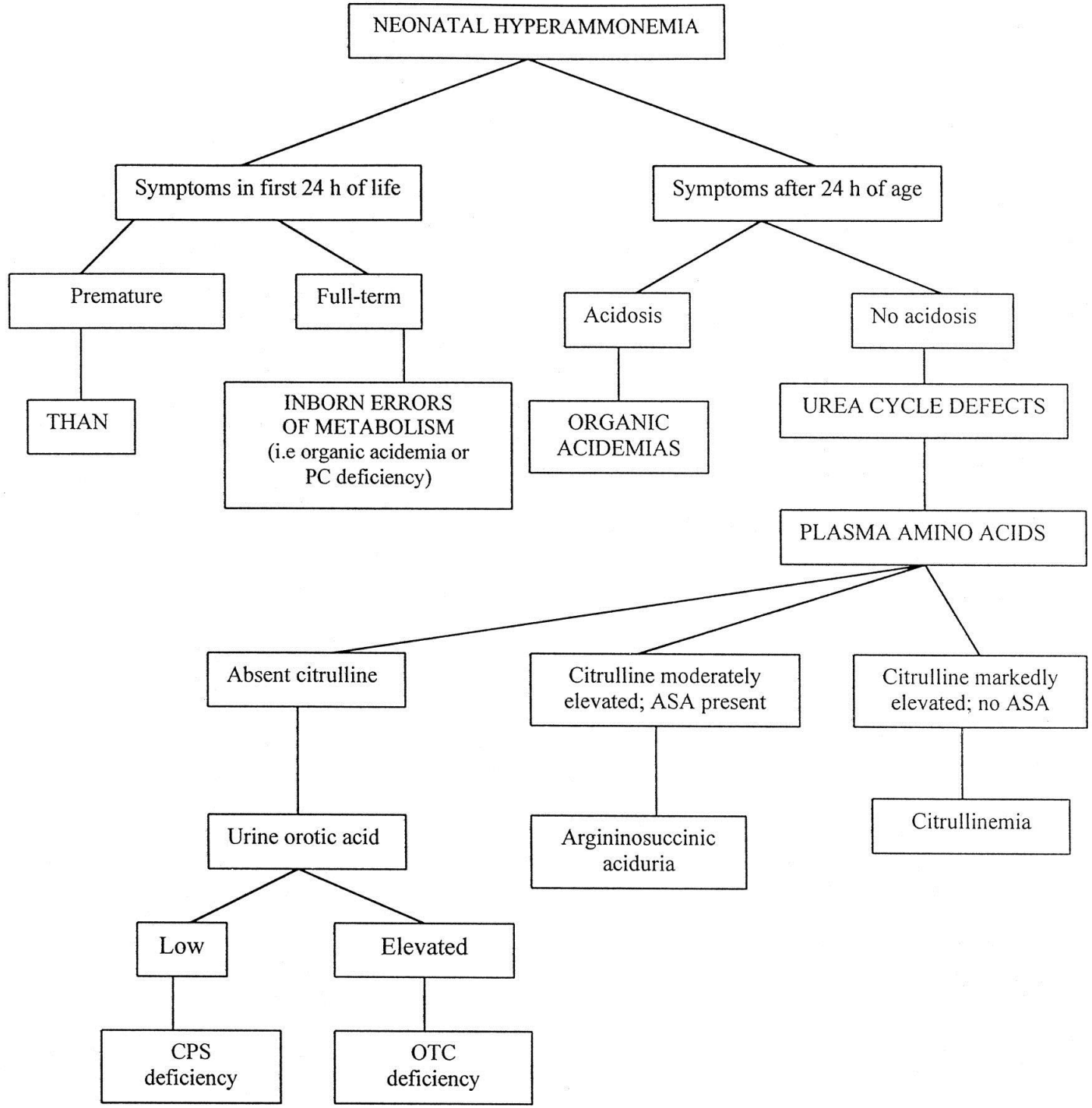
Organic acidemias, glycogen storage disease 1b, respiratory chain defects

Ammonia

Organic acidemias, **urea cycle defects,** transient ammonia of the neonate


METABOLIC ACIDOSIS WITH INCREASED ANION GAP
Normal lactate
Elevated lactate
Abnormal organic acids
Normal organic acids
ORGANIC ACIDEMIA
Abnormal organic acids
Elevated pyruvate: normal L-P ratio
Normal or low pyruvate elevated L-P ratio
Hypoglycemia
No hypoglycemia
RESPIRATORY CHAIN DEFECTS; PYRUVATE CARBOXYLASE DEFICIENCY
Dicarboxylic aciduria
METHYLMALONIC ACIDEMIA; PROPIONIC ACIDEMIA; MULTIPLE CARBOXYLASE DEFICIENCY; OTHERS
FATTY ACID OXIDATION DEFECTS
GSD TYPE I; FRUCTOSE 1,6-DP DEFICIENCY; PEP CARBOXYKINASE DEFICIENCY
PYRUVATE DEHYDROGENASE DEFICIENCY; PYRUVATE CARBOXYLASE DEFICIENCY

Burton et al, 1998



QUESTION

An newborn infant present with lethargy and poor feeding in the first day of life. Negative infectious work up. Head imaging shows no evidence of IVH, stoke or mass. Serum ammonia is 300 μM/L with **normal** concentrations of lactate and amino acid. The urine does not contain ketones and has normal organic acid levels.

Of the following, the infant in this vignette most likely has:

A. Arginase Deficiency (Urea Cycle Defect)
B. Glutaric Aciduria (Disorder of Protein Metabolism)
C. Methylmalonic Acidemia (Organic Acidemia)
D. Ornithine Transcarboxylase Deficiency (Urea Cycle Defect)
E. Transient Neonatal Hyperammonemia

INBORN ERRORS OF METABOLISM

Carbohydrate Metabolism Disorder
Galactosemia
Glycerol Kinase Deficiency
Glycogen Storage Diseases

Organic Acid Disorders
Propionic Acidemia
Isovaleric Acidemia
Methylmalonic Acidemia

Amino Acid Disorders
Phenylketonuria
Tyrisonemia
Maple Syrup Urine Disease
Nonketotic Hyperglycinemia
Homocystinuria
Glutaric Acidemia Type I

Urea Cycle Defects
CPS Deficiency
OTC Deficiency
Citrillinemia
Argininosuccinic Aciduria
Argininemia

Inborn Errors of Metabolism Categories		Incidence/ Inheritance	Enzyme Deficiency	Symptom Onset	FL State Newborn Screen
Disorders of Carbohydrate Metabolism	Galactosemia	1:40,000 AR	1. Galactose-1-Phosphate Uridyltransferase (GALT) 2. Galactose epimerase	First few days of life	Yes
	Glycogen Storage Disease (Von Gierke)	1:100,000 AR	Glucose-6 -Phosphatase	By 2 years of age	No
Disorders of Amino Acid Metabolism	Phenylketonuria (PKU)	1:15,000 AR	1. Phenylalinine Hydroxylase 2. Biopterin defect	First few months of life	Yes
	Maple Syrup Urine Disease	1:150,000 AR	Branched chain 3-Ketoacid Dehydrogenase Complex	3-5 days of age	Yes
	Tyrosinemia type I	Rare AR	Fumarylacetoacetate hydroxylase	Birth to first few months of life	Yes
	Glutaric Acidemia	1:30-40,000 AR	Glutaryl-CoA Dehydrogenase	Infancy or early childhood	Yes
	Urea Cycle Defects	1:30,000		Varies	Some

CARBOHYDRATE METABOLISM DISORDERS

A CASE TO REMEMBER

- 7 day old female infant transferred from OSH for evaluation of poor feeding, vomiting and abdominal distention. Required treatment for hyperbilirubinemia (total bili 15.4) at 4 days of life. Labs prior to NICU admission were normal except mild transaminitis (AST 156 and ALT 188 U/L) and transient elevation in ammonia (202 µg/dl). Ammonia normal when rechecked on admission. Sepsis work up was negative.

- **Birth History:** Born at 37 weeks GA via SVD. Of note, mother had epilepsy, which was treated with Carbamazapine throughout pregnancy.

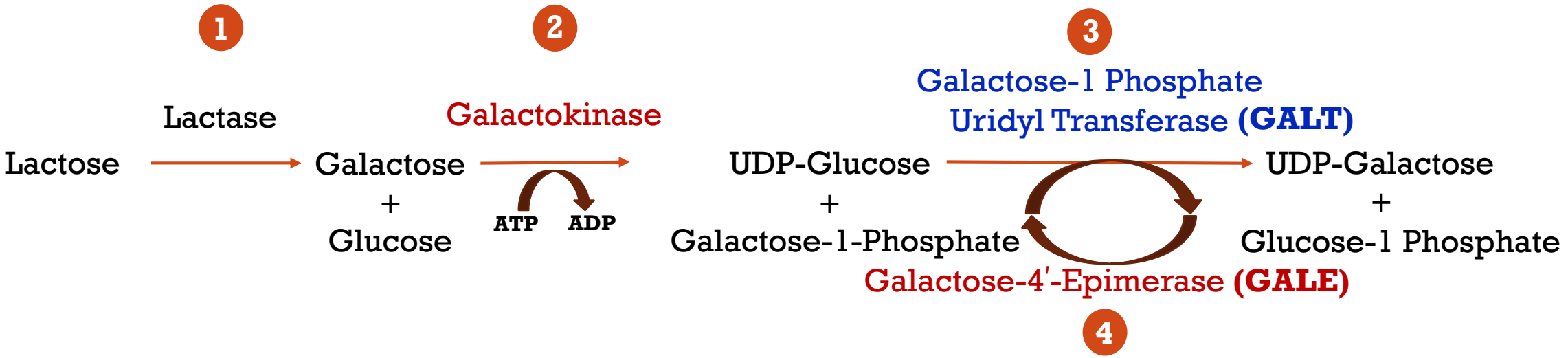
- **NICU Management:** For 9 days, low-protein, lactose-free, hydrolysate formula due to concern for cow's milk intolerance. Progressive clinical improvement and normal labs. At the age of 16 days, a standard formula feeding was re-introduced, still with a reduced intake of proteins. Again, vomiting and anorexia occurred, further supporting the hypopthesis of cow's milk intolerance. Thus, the same protein hydrolysate formula used earlier was resumed and continued in the following months.

Which metabolic disorder should also be considered?

GALACTOSEMIA

- **Autosomal recessive** disorder of galactose metabolism
- 1/40,000 live births in the US
- **Three forms:** Classic galactosemia, Galactokinase deficiency, Galactose-4′-epimerase deficiency
- **Screening** (Most US states use a combination of these approaches)
  - Measures GALT activity* &/OR Galactose and Galactose-1-Phosphate
- **Clinical Presentation:** Lethargy, poor feeding, jaundice, **cataracts**, ***E. coli*** **sepsis**
- **Laboratory findings:** ↓glucose, ↑ LFTs, ↑ total bilirubin, hyperchloremic metabolic acidosis*, normal lactate, normal pyruvate
- **Diagnostic Test**
  - Urinary reducing substances*
  - Whole blood or erythrocyte GALT activity and erythrocyte red cell galactose-1-phosphate
- **Treatment:** Strict dietary lactose /galactose restriction
- **Long term Prognosis:** Mild growth failure, learning disabilities, ataxia, tremor and verbal dyspraxia
  - Ovarian failure, probable infertility in males also

GALACTOSEMIA PATHWAY



Diagnosis in Absence of Enzyme

1. Lactose intolerance
2. Galactokinase — Cataracts (late in childhood)
3. Classic Galactosemia
4. Galactose-4′-Epimerase Deficiency

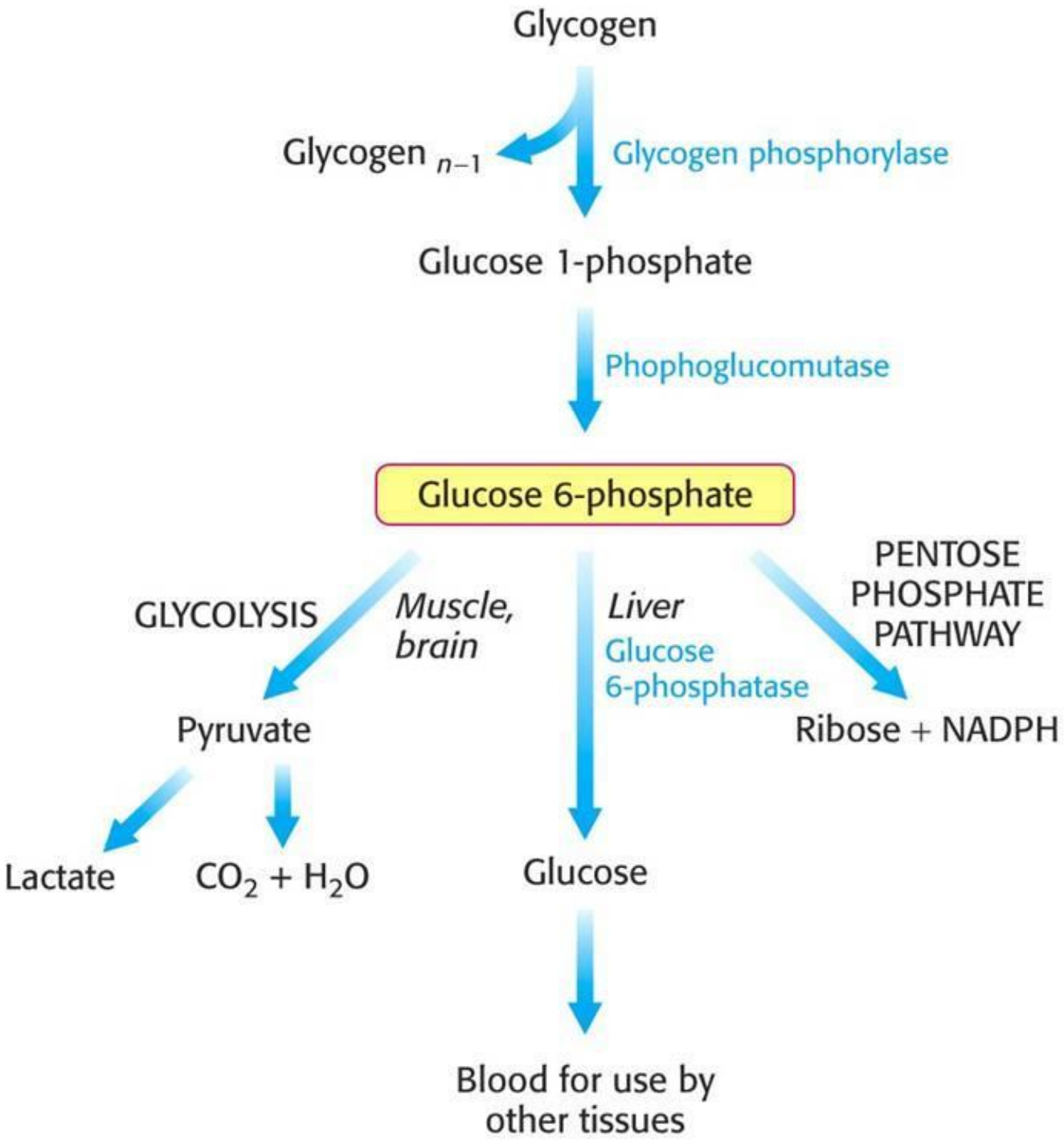
Cataracts, FTT, diarrhea, jaundice, intellectual disability and liver failure (first few months of life)

GLYCEROL KINASE DEFICIENCY

- **X-linked recessive** defect in glycerol kinase
- **FL State Newborn Screen NO**
- **Clinical Presentation:** Can present in neonatal period: cyptorchidism, seizures, strabismus.
  - **Isolated Symptomatic: Lethargy, vomiting, acidosis, ketotic hypoglycemia**
  - **Isolated Benign**
  - **Complex (Deletion Syndrome): Glycerol Kinase Deficiency, Adrenal Hypoplasia and Duchenne Dystrophy**
- **Lab Findings:** Pseudotriglyceridemia (elevated glycerol interferes with assay for triglycerides)
- **Diagnostic studies: FISH analysis to assess for deletion**
  - **Glycerol kinase gene near dystrophin and congenital adrenal hypoplasia gene**
- **Treatment:** Manage SYMPTOMS as indicated by using corticosteroids, glucose infusion, or mineralocorticoids
  - No permanent treatment available
- **PROGNOSIS:** Infantile form is associated with severe developmental delay

GLYCOGEN STORAGE DISEASE

Type	Enzyme defect	Eponym	Hypoglycemia	Hyperlipidemia	Symptoms	Others
GSD type 1	Glucose-6-phosphatase	Von Gierke's	Yes	Yes	Growth failure	Lactic acidosis, hyperuricemia
GSD type 2	Acid maltase	Pompe's	No	No	Death by age ~ 2 years	Heart failure Myopathy
GSD type 3	Glycogen debrancher	Cori's or Forbes'	Yes	Yes		Myopathy
GSD type 4	Glycogen branching enzyme	Andersen	No	No	Failure to thrive, death at age ~ 5 years	Liver cirrhosis
GSD type 5	Muscle glycogen phosphorylase	McArdle	No	No		Renal failure by myoglobinuria
GSD type 6	Liver glycogen phosphorylase	Hers' disease	Yes	No		
GSD type 7	Muscle phosphofructokinase	Tarui's disease	No	No	Growth retardation	Hemolytic anemia
GSD type 9	Phosphorylase kinase PHKA2		No	Yes	Delayed motor development, growth retardation	
GSD type 11	Glucose transporter GLUT2	Fanconi-Bickel Syndrome	Yes	No		
GSD type 12	Aldolase A	Red cell aldolase deficiency	?	?		Exercise intolerance
GSD type 13	B-enolase		?	?		Exercise intolerance

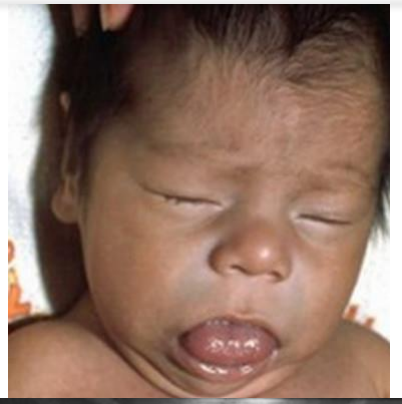

Glycogen
Glycogen $_{n-1}$
Glycogen phosphorylase
Glucose 1-phosphate
Phophoglucomutase
Glucose 6-phosphate
GLYCOLYSIS
Muscle, brain
Liver
Glucose 6-phosphatase
PENTOSE PHOSPHATE PATHWAY
Pyruvate
Ribose + NADPH
Lactate
$CO_2 + H_2O$
Glucose
Blood for use by other tissues

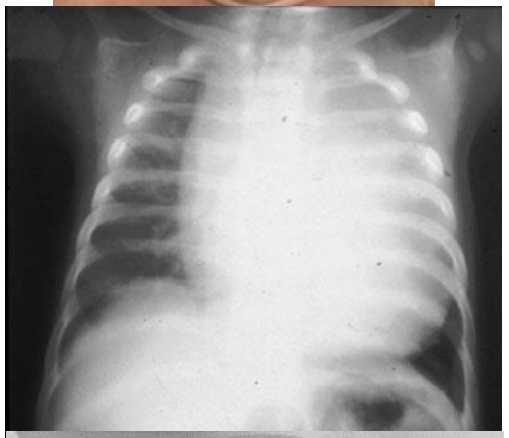
VON GIERKE DISEASE (GSD 1A)

- **Autosomal recessive** defect in **glucose-6-phosphatase** → glycogen accumulates in the liver
- **FL State Newborn Screen NO**
- **Clinical Presentation:** Normal at birth. Hypoglycemia presents when infants start to sleep through the night (prolonged fasting). Hepatomegaly
  - May present in neonatal period
- **Lab Findings: Hypoglycemia**, lactic acidosis, ↑urea, ↑ lipids and triglycerides
- **Diagnostic studies**
  - Liver biopsy glycogen and assay for enzyme
  - DNA testing may obviate need for liver biopsy
- **Treatment:** Avoidance of fasting. Continuous nighttime feeds in infancy. Corn starch.

POMPE DISEASE (GSD 2)

- **Autosomal recessive** disorder of α 1,4-glucosidase
- **FL State Newborn Screen NO**
- **Clinical Presentation:** Normal at birth. Then onset of muscle weakness, feeding and breathing difficulty
  - Infantile: dilated cardiomyopathy, failure to thrive, hypotonia, macroglossia
- **Lab Findings: NO hypoglycemia!!!,** ↑CPK
- **Diagnostic studies:** Assay enzyme in lymphocytes, muscle or fibroblasts
- **Treatment:** Enzyme Replacement Therapy available since 2006





QUESTION

An infant presents in the newborn period with lactic acidosis, hypoglycemia and hepatomegaly. Further testing reveals the infants has gylcogen storatge disease.

Of the following, the enzyme that is most likely to be deficient in this infant is:

A. Branch enzyme
B. Debranching Enzyme
C. Glucose-6-Phosphate
D. Lysosomal Alpha-Glucosidase
E. Phosphorylase kinase

DISORDERS OF PROTEIN METABOLISM

PHENYLKETONURIA (PKU)

- **Autosomal recessive** disorder in which phenylalanine can not be converted to tyrosine
- 1/10-20,000 live births in the US
- **Enzyme Defect:** Phenylalanine Hydroxylase (chromosome 12q24.1)
- **Clinical Presentation:** Normal at birth. > 50% affected infants present with the following signs:
  - Vomiting, irritability, eczematoid rash, peculiar odor 'musty', fair-hair and skin
- **Screening** (In all 50 states)
  - Test for elevated levels of phenylalanine

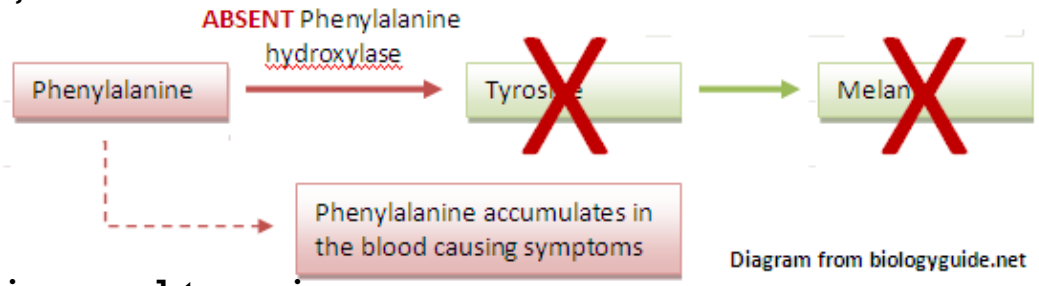
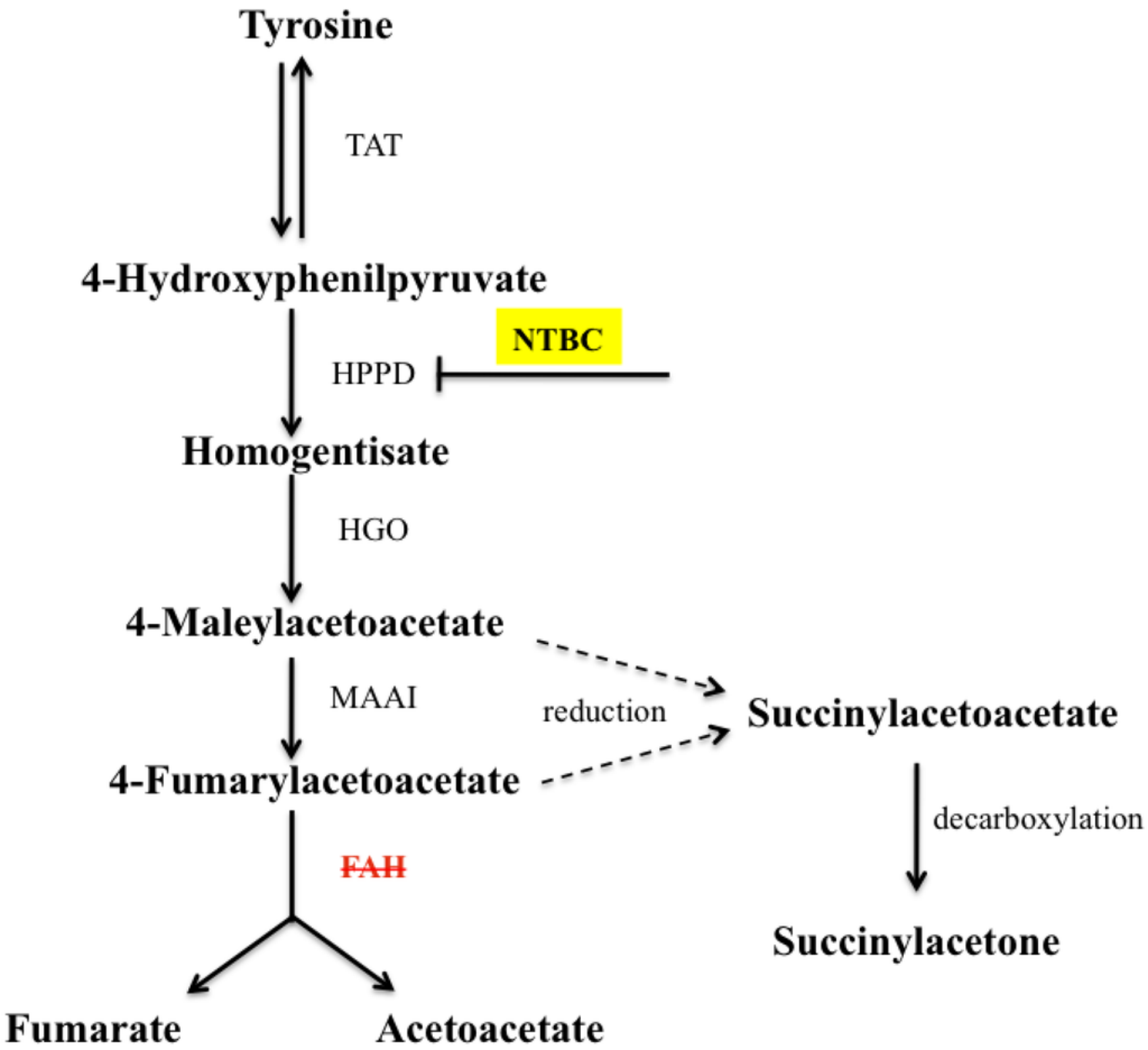


Diagram from biologyguide.net

- **Diagnostic studies**
  - If positive screen, quantitative analysis of serum phenylalanine and tyrosine
- **Treatment:** Limit dietary intake of phenylalanine.
  - Followed by dietician and Phe levels are monitored closely
- **Long term Prognosis:** If untreated severe intellectual disability IQ < 30. Acquired microcephaly
  - Damage becomes irreversible by 8 weeks of age

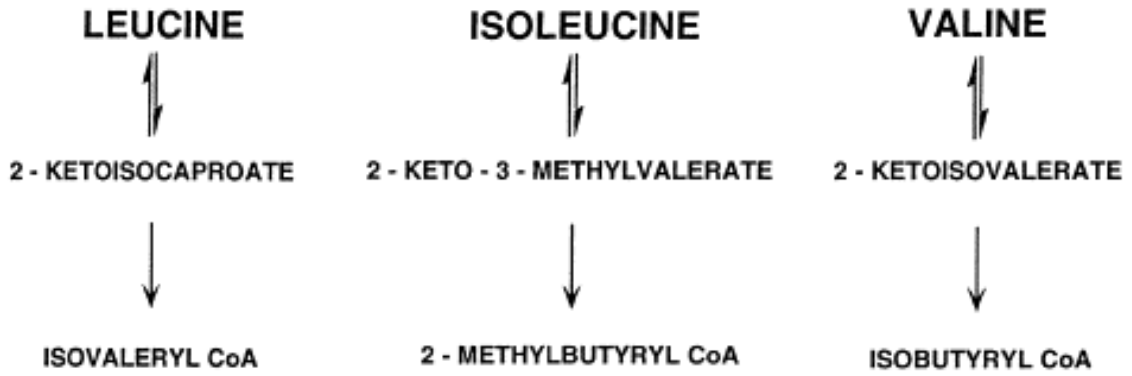
TYROSINEMIA

	Enzyme Defect	Clinical Presentation	Diagnostic Studies	Treatment	Prognosis	FL State Newborn Screen
Type I	Fumarylacetoacetate hydroxylase	Failure to thrive (FTT) Hepatomegaly Hepatoblastoma RTA Rickets	Succinylacetone in urine ↑ levels of tyrosine in plasma	Diet low in tyrosine and phenylalanine -NTBC	Infants are affected early with high risk of mortality	Yes
Type II	Tyrosine Aminotransferase	Corneal ulcers or dendritic keratitis 50% with intellectual disability Red papular lesions on their palms and soles No liver toxicity		Diet low in tyrosine	Diet may not be curative	Yes


Tyrosine
TAT
4-Hydroxyphenilpyruvate
NTBC
HPPD
Homogentisate
HGO
4-Maleylacetoacetate
MAAI
reduction
Succinylacetoacetate
4-Fumarylacetoacetate
decarboxylation
FAH
Succinylacetone
Fumarate
Acetoacetate

MAPLE SYRUP URINE DISEASE

- **Autosomal recessive** disorder of branched chain amino acid metabolism (valine, leucine and isoleucine
- ~ 1/150,000 live births in the US (1:1000 Mennonites)
- **Enzyme Defect:**
  - Defect in **oxidative decarboxylation of ketoacids**
- **FL State Newborn Screen** YES



- **Clinical Presentation:** Feeding difficulty, irregular respirations, loss of Moro reflex, bicyclinc motion of legs/swimming with arms, severe seizures, opisthotonos and rigidity
- **Diagnostic Test**
  - Plasma amino acid: ↑ leucine, isoleucine & valine
  - Urine organic acids – branched chain 2-keto and 2-hydroxy acids
  - Presence of **alloisoleucine** is diagnostic
- **Treatment:** Strict dietary control of leucine, isoleucine and valine restriction
  - Rare form that responds to Thiamine
- **Long term Prognosis:**
  - Rapid progression to death within 2-4 weeks in no treatment initiated
  - If early therapy normal IQ is possible

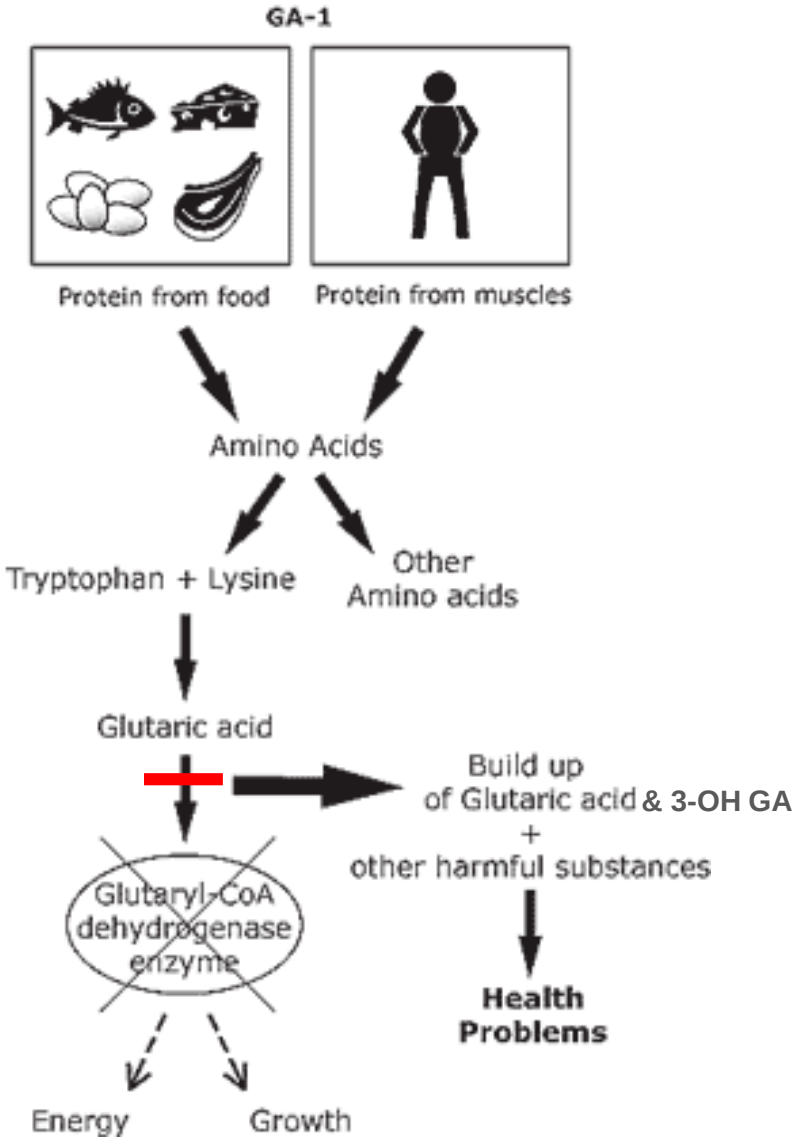
A CASE TO REMEMBER

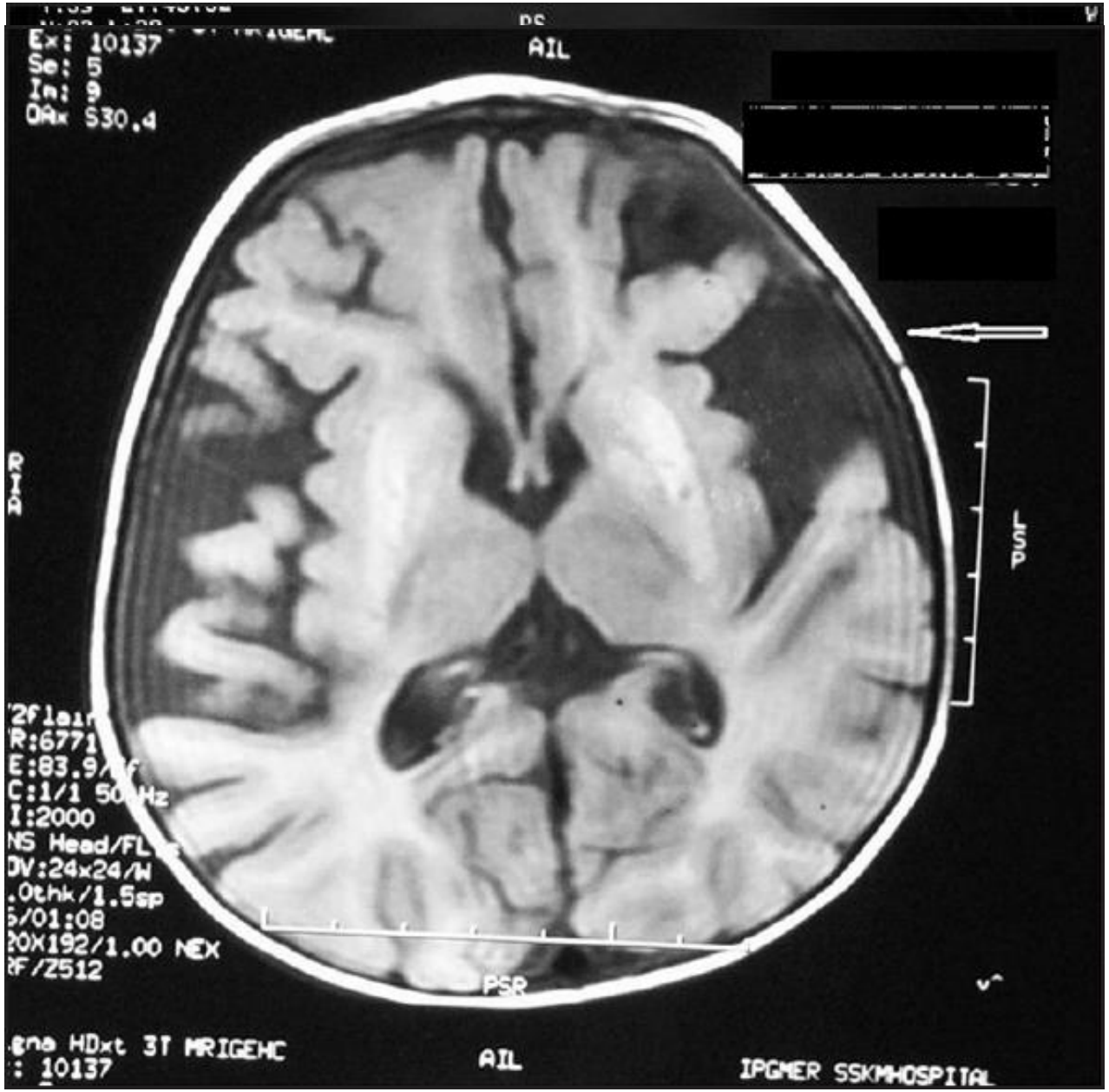
- A 7-month-old female is transferred from OSH for further evaluation of persistent seizures and dystonia following acute pyogenic meningitis.
- She was diagnosed with meningitis after presenting with fever, vomiting, irritability, and generalized seizures
  - CSF fluid analysis: 8 WBC cells/μL (All Lymphocytes), Protein 52 g/dl, and Glucose 62 mg/dl.
  - OSH **CT brain** bilateral arachnoid cyst
- **BIRTH HISTORY:** Born term via SVD was
- **DEVELOPMENTAL HISTORY:** Reaching milestones appropriately

What additional information is needed?

GLUTARIC ACIDEMIA TYPE 1

- **Autosomal recessive** disorder resulting in defect in the catabolic pathway of lysine, hydroxylysine and tryptophan
- 1/30-40,000 live births in the US
- **Enzyme Defect:** Glutaryl-CoA Dehydrogenase (on chromosome 19)
- **FL State Newborn Screen:** YES
- **Clinical Presentation:** Macrocephaly at birth, normal development until illness or metabolic stressor → hypotonia and dystonia 'mimics acute onset CNS infection*
  - CT/MRI brain findings are present at birth (see images next)
  - Can cause subdural hematomas and retinal hemorrhages
- **Diagnostic Test**
  - Urine organic acids: ↑ glutaric acid and 3-hydroxyglutaric acids
    - Plasma **carnitine** levels are low
  - Prenatal diagnosis: increased concentrations of glutaric acid in amniotic fluid – DNA test preferred
- **Treatment:** L-carnitine, riboflavin and special diet
  - When acutely ill provide IV fluids containing glucose
- **Long term Prognosis:** Mild growth failure, learning disabilities and verbal dyspraxia
  - 5% of patients will be asymptomatic
  - 35% of patients will have severe disease despite optimal therapy



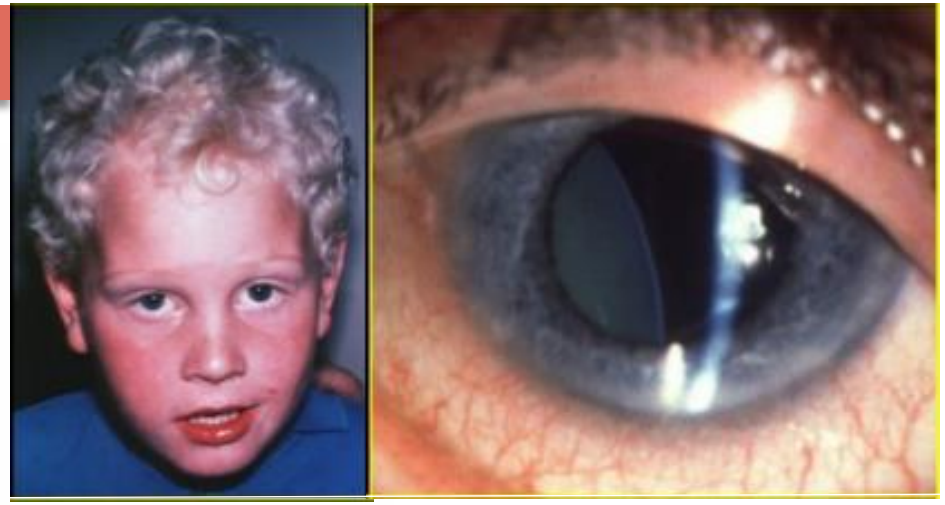


GLUTARIC ACIDEMIA TYPE 1

HOMOCYSTINURIA

- **Autosomal recessive** disorder of methionine metabolism
- 1/200-335,000 live births worldwide
  - Ireland (1 in 65,000), Germany (1 in 17,800), Norway (1 in 6,400), and Qatar (1 in 1,800).
- **Enzyme Defect:** Cystathionine β-synthetase (chromosome 21q)
- **Screening** YES (Elevated methionine)
- **Clinical Presentation:** Marfanoid habitus, developmental delay, downward /medial lens dislocation, osteoporosis and increased risk of arterial/venous thromboembolism
  - Presents within first 10 years
- **Diagnostic Test**
  - Blood and urine test for excess homocysteine and methionine. Low level of cysteine
  - Liver biopsy and enzyme assay for enzymatic activity
- **Treatment:** Large doses of pyridoxine (B6), B12 and folic acid. Diet low in methionine
  - Supplementation with Betaine
- **Long term Prognosis:** Intellectual disability is fairly common

HOMOCYSTINURIA PATHWAY



Methionine* ↑

S-adenosyl methionine

↑ Homocystine (urine) ⟷ Homocysteine ↑

Cystathionine β synthase ↓ *(Vit B_6 – activated)*

Cystathionine

Cystathionine lyase (Vit B6 – activated)

Cysteine ↓ → Glutathione ↓ → Cataract

Cystine** ↓

A CASE TO REMEMBER

- 2-day-old male infant is transferred from Newborn Nursery with lethargy, poor feeding, and frequent **hiccups**.
- **Birth History:** Born at term via SVD. Pregnancy was uneventful.
  - Birth weight - 3.2 kg (50th %ile) and Head circumference - 35 cm (50th %ile)
- **Admission Examination:** Gross hypotonia, poor suck, weak cry and no dysmorphic features.
- NICU course:
  - **Apneic episodes** requiring ventilatory support. No spontaneous breathing was observed while on ventilator despite not being on sedation.
  - Later noted to have some **abnormal movements** including jitteriness, hiccups, and twitching of his limbs for which he was treated with phenobarbitone.

1. Create a Differential Diagnosis.

2. Order laboratory test to narrow the Differential.

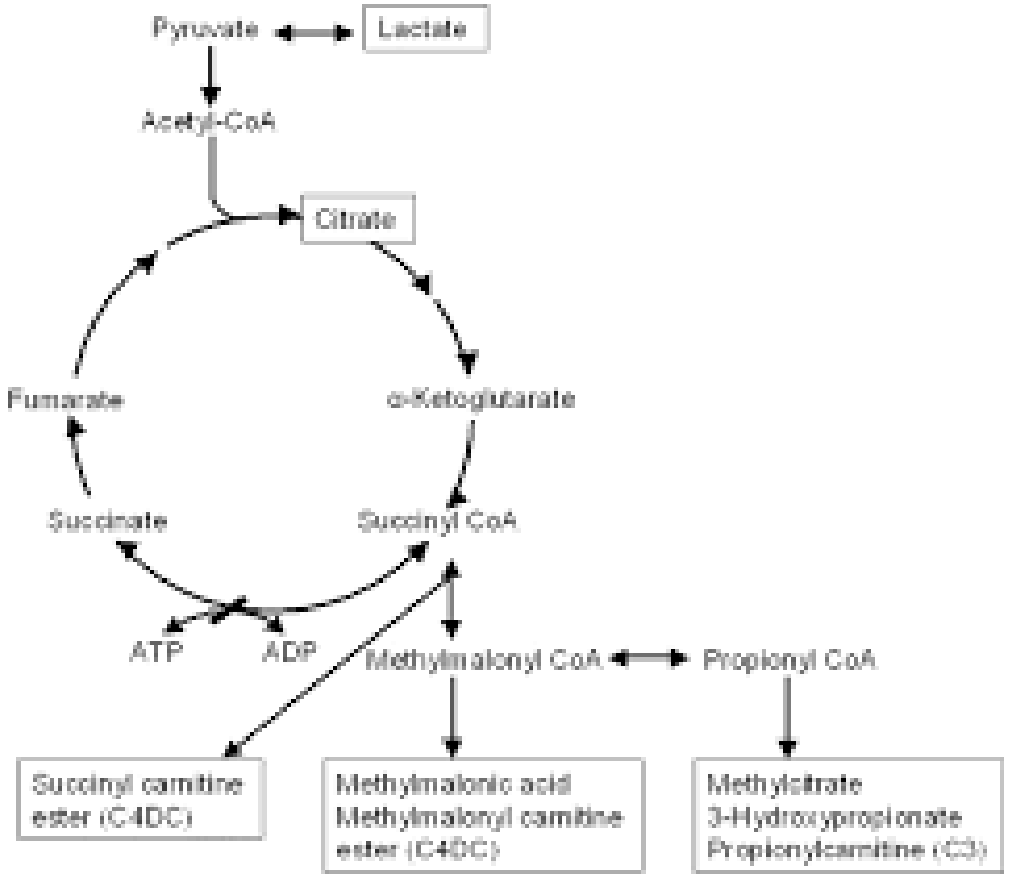
NONKETOTIC HYPERGLYCINEMIA

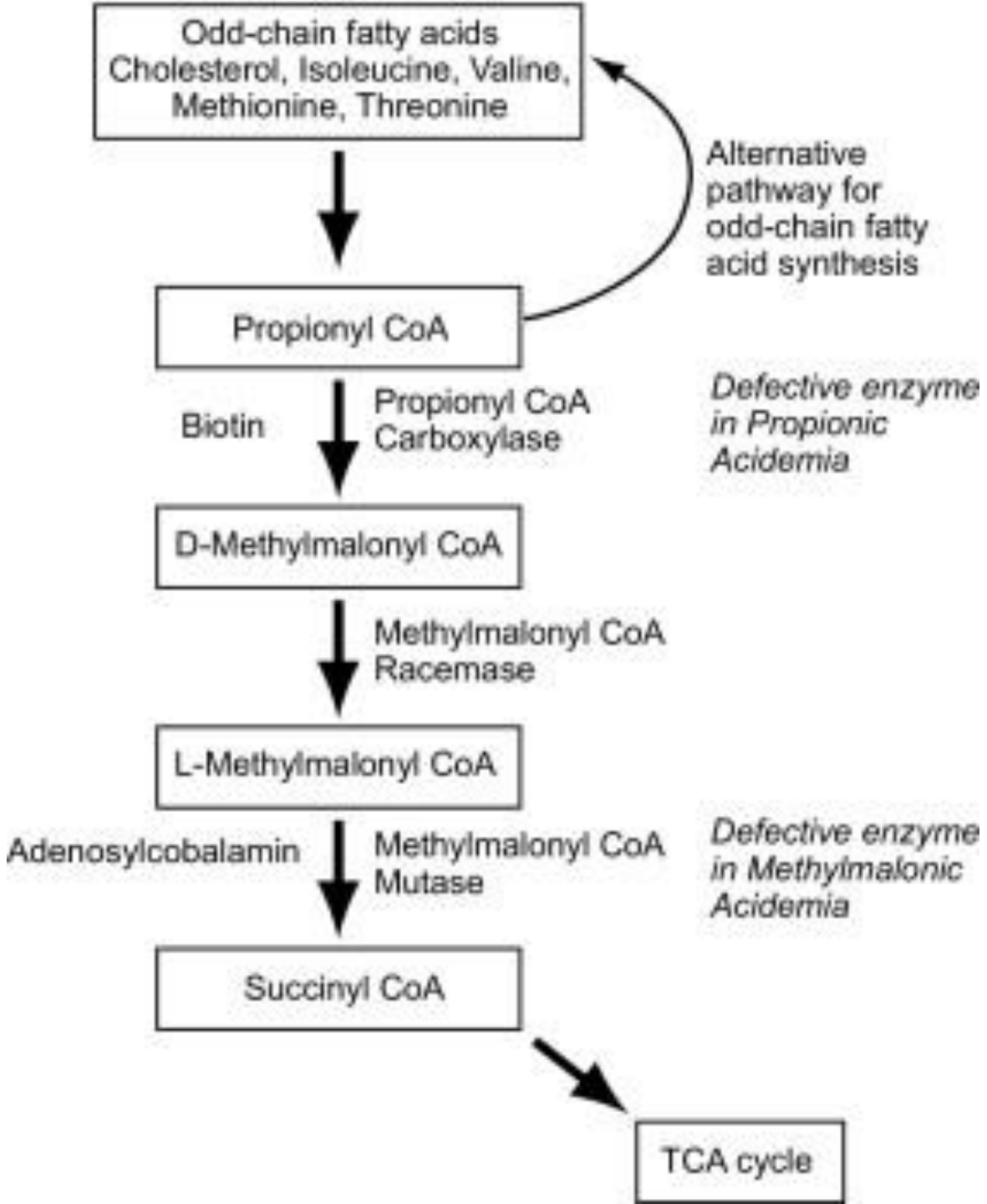
- **Autosomal recessive** disorder of gylcine metabolism
- 1/250,000 in the US
- **Enzyme Defect:**
  - More than 80% of patients have a defect in P-protein of glycine cleavage enzyme
- **Clinical Presentation:** Neonatal hiccups, myoclonic seizures and altered consciousness
  - Neonatal: presents in 1st week of life
  - Infantile: presents by 6 months of age. Seizures
  - Late onset: present 2-33 years of age. progressive spastic paraparesis, choreoathetosis, and optic atrophy
- **Screening** (Most US states use a combination of these approaches) ***
- **Diagnostic Test**
  - Hyperglycinemia and elevated CSF glycine levels in the absence of an organic acid disorder
    - CSF and plasma glycine measurements are essential for the diagnosis of NKH, CSF/plasma glyceine ratio > 0.08
  - Glycine cleavage enzyme assays on liver biopsy **(GOLD STANDARD)**
  - Prenatal diagnosis: GCS enzyme assay in chorionic villi
- **Treatment:** Sodium Benzoate → reduce CSF glycine → Decrease seizures
  - Dextromoethorphan has also been used with some success
- **Long term Prognosis:** Poor prognosis. Often fatal

Igbal et al, 2015


http://www.parkwaypeds.com/wp-content/uploads/2015/03/c4ca4238a0b923820dcc509a6f75849b1.jpg

ORGANIC ACID DISORDERS


Pyruvate
Lactate
Acetyl-CoA
Citrate
Fumarate
α-Ketoglutarate
Succinate
Succinyl CoA
ATP
ADP
Methylmalonyl CoA
Propionyl CoA
Succinyl carnitine ester (C4DC)
Methylmalonic acid
Methylmalonyl carnitine ester (C4DC)
Methylcitrate
3-Hydroxypropionate
Propionylcarnitine (C3)


Odd-chain fatty acids
Cholesterol, Isoleucine, Valine, Methionine, Threonine
Alternative pathway for odd-chain fatty acid synthesis
Propionyl CoA
Biotin
Propionyl CoA Carboxylase
Defective enzyme in Propionic Acidemia
D-Methylmalonyl CoA
Methylmalonyl CoA Racemase
L-Methylmalonyl CoA
Adenosylcobalamin
Methylmalonyl CoA Mutase
Defective enzyme in Methylmalonic Acidemia
Succinyl CoA
TCA cycle

PROPIONIC ACIDEMIA

- **Autosomal recessive** defect in propionyl CoA carboxylase
- **FL State Newborn Screen** YES
- **Clinical Presentation:** Neonatal onset: Lethargy and coma
- **Lab Findings: ↑↑ammonia,** anion gap metabolic acidosis, neutropenia, thrombocytopenia, hyperglycinemia
- **Diagnostic Test**
  - Elevated propionyl carnitine.
  - Plasma amino acid: ↑ Glycine
  - Urine organic acid: ↑ Methylcitrate
  - Enzyme assay on leukocytes
- **Treatment:**
  - **Diet**
  - **Carnitine**
  - **Biotin (Cofactor for enzyme)**

ISOVALERIC ACIDEMIA

- **Autosomal recessive** defect in leucine metabolism
- 1:230,000 live births
- **Enzyme Defect:** Isovaleryl-CoA dehydrogenase deficiency
- **Clinical Presentation: "Odor of sweaty feet"** 
  - Onset in newborn periods – severe metabolic acidosis, ketosis with vomiting → coma and death
  - Onset in infancy (more common) – symptoms are preceded by an infection or increased protein intake
    - Subsequent chronic intermittent pancytopenia and acidosis
- **FL State Newborn Screen** YES
- **Diagnostic Test**
  - Urine organic acids
  - Prenatal diagnosis is possible
- **Treatment:**
  - **Acute:** IV glucose
  - **Chronic:** Restricting leucine intake and prescribing carnitine &/or glycine

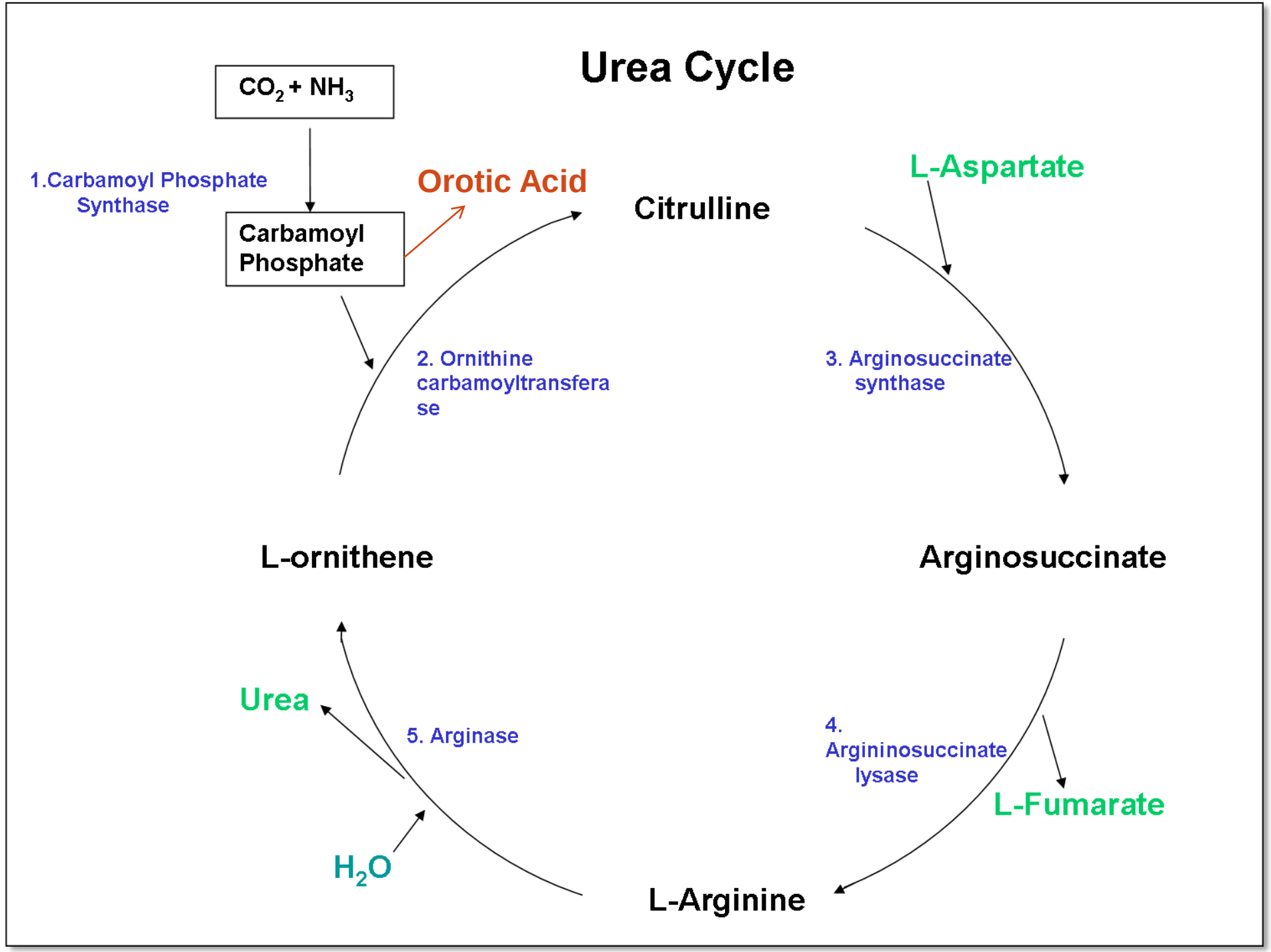
METHYLMALONIC ACIDEMIA

- **Autosomal recessive** disorder that ultimately inhibits methylmalonyl-CoA mutase function.
- 1/55,000 live births in the Finland
- **Enzyme Defect:** Mutase deficiency and Cobalamin A, B, C, D, F and X deficiency
- **Clinical Presentation:** Early: hyperammonemia, ketoacidosis and thrombocytopenia
  - Late onset: complication is renal failure and cardiomyopathy
- **FL State Newborn Screen** YES
- **Diagnostic Test**
  - **Urine organic acids (increased methylmalonic acid and abnormal ketone bodies)**
  - **Elevated homocysteine levels**
- **Treatment:** Restriction of dietary protein. Betaine and IM B_{12} vitamin only for cobalamin C, E and some D deficiencies
  - Liver and kidney transplants may be curative


http://i.huffpost.com/gen/1151797/images/o-CRACK-BABIES-facebook.jpg

UREA CYCLE DEFECTS

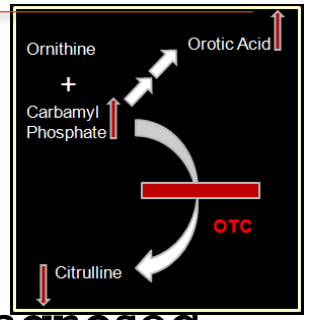
Urea Cycle Defects	Incidence/ Inheritance	Deficiency	Symptom Onset	Presentation	Labs	FL State Newborn Screen
CPS Deficiency	1:70-100,000 AR	Carbamoyl phosphate synthetase I	By 5 days of age	Lethargy, hypotonia, vomiting and poor feeding Death if undiagnosed	**↑Ammonia** ↑CSF Glutamine Respiratory alkalosis Low BUN ↑Glutamine, alanine, asparagine ↓Citrulline ↓Argninine ↓Urine orotic acid	NO
Ornithine Transcarbamylase (OTC) Deficiency	1:70,000 X-linked (Most common)	Ornithine Transcarbamylase	24-48 hours	Lethargy, hypotonia, vomiting and poor feeding Death if undiagnosed	**↑Ammonia** ↑CSF Glutamine Respiratory alkalosis Low BUN ↑Glutamine, Alanine, Asparagine ↓Citrulline ↓Argninine ↑Urine orotic acid	NO
Citrillinemia	AR	Arginoinosuccinate synthetase deficiency	Late onset; preceded by stressor		**↑Ammonia** ↓Argninine	Yes
Argininosuccinic Aciduria	AR	Argininocuccinate lyase deficiency	Late onset; preceded by stressor	Trichorrhexis nodosa Episodic coma	**↑Ammonia** ↓Argninine	Yes
Argininemia	AR	Arginase deficiency	Late onset; preceded by stressor	Progressive splastic diplegia, tremor, ataxia	**↑Ammonia** Normal Argninine	


Urea Cycle
$CO_2 + NH_3$
1.Carbamoyl Phosphate Synthase
Carbamoyl Phosphate
Orotic Acid
Citrulline
L-Aspartate
2. Ornithine carbamoyltransfera se
3. Arginosuccinate synthase
L-ornithene
Arginosuccinate
Urea
5. Arginase
H_2O
4. Argininosuccinate lysase
L-Fumarate
L-Arginine

CPS DEFICIENCY

- **Autosomal recessive** disorder of amino acid metabolism
- 1:150-200,000 live births.
- **Enzyme Defect:** Carbamoyl phosphate synthetase (CPS) I
- **Clinical Presentation:** sleepiness, poorly regulated breathing rate or body temperature, unwillingness to feed, vomiting after feeding, unusual body movements, seizures, or coma
  - **Severe:** Onset within first few days after birth
  - **Mild:** Onset later in life
- **Florida State Newborn Screen** NO
- **Lab Findings:** ↑**Ammonia,** ↑CSF Glutamine, Respiratory alkalosis, Low BUN, ↑Glutamine, alanine, asparagine, ↓Citrulline ↓Argninine, ↓**Urine orotic acid**
- **Diagnostic Test**
  - **Ammonia**
  - **Plasma and urinary organic acids**
- **Treatment:** Protein restricted diet
  - Acute: If infant in a coma & plasma ammonia > 500 μM/L, hemodialysis is the only way to clear ammonia
  - Chronic: High calorie, protein restricted diet with or without additional amino acids
    - Infantile onset has increasing patients undergoing liver transplants with improved outcomes
- **Long term Prognosis:** Survival beyond newborn period: recurrence of elevated ammonia. Delayed development and intellectual disability

ORNITHINE TRANSCARBOMYLASE (OTC) DEFICIENCY



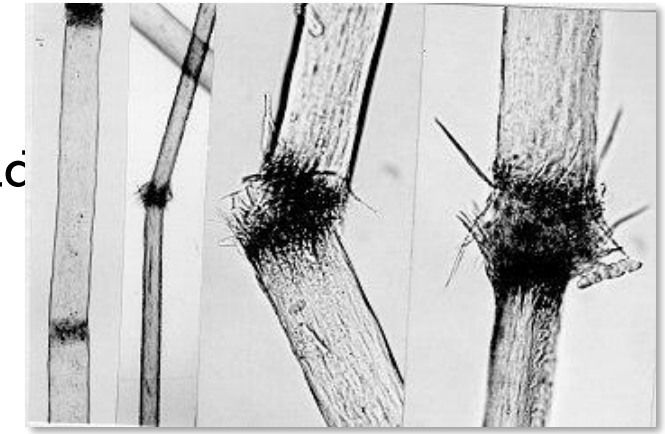
- **X-linked** disorder of nitrogen waste removal
- 1: 70,000 (most common Urea Cycle Defect)
- **Enzyme Defect:** Ornithine Transcarbamylase (chromosome Xp11.4)
- **Clinical Presentation:** Lethargy, hypotonia, vomiting and poor feeding. Death if undiagnosed
- **Lab Findings:** ↑**Ammonia** (> 700 μM/L), ↑CSF Glutamine, Respiratory alkalosis, Low BUN, ↑Glutamine, Alanine, Asparagine, ↓Citrulline, ↓Argninine, ↑**Urine orotic acid (diagnostic)**
- **FL State Newborn Screen** NO
- **Diagnostic Test**
  - Ammonia
  - Quantitative plasma and urinary organic acids
- **Treatment:**
  - Acute: If infant in a coma & plasma ammonia > 200 μM/L, hemodialysis is the only way to clear ammonia
  - Chronic: High calorie, protein restricted diet with or without additional amino acids
    - Infantile onset has increasing patients undergoing liver transplants with improved outcomes
- **Long term Prognosis:** Affected first born males usually die, or severely impaired.
  - Females can manifest milder, clinically significant disease.

CITRILLINEMIA

- **Autosomal recessive** defect in ASS
- 1/57,000 live births in the US
- **Enzyme Defect:** Arginoinosuccinate synthetase (ASS)
- **FL State Newborn Screen** Yes **(**↑↑↑ citrulline**)**
- **Clinical Presentation:** Infants with the acute neonatal form appear normal at birth. Shortly thereafter, they develop hyperammonemia and become progressively lethargic, feed poorly, often vomit, and may develop signs of increased intracranial pressure (ICP).
- **Lab Findings:** ↑↑↑ citrulline (>1000 µmol/L) ↑ammonia (> 150 µM/L), ↑orotic acid (not as high as OTC), ↓arginine
- **Diagnostic Test**
  - Ammonia, Quantitative plasma and urinary organic acids
- **Treatment:** Arginine
  - Acute: If infant in a coma & plasma ammonia > 200 µM/L, hemodialysis is the only way to clear ammonia
  - Chronic: High calorie, protein restricted diet with or without additional amino acids
- **Prognosis:**
  - Without prompt intervention, hyperammonemia and the accumulation of other toxic metabolites (e.g., glutamine) result in increased ICP, increased neuromuscular tone, spasticity, ankle clonus, seizures, loss of consciousness, and death.
  - Children with the severe form who are treated promptly may survive for an indeterminate period of time, but usually with significant neurologic deficits.

ARGININOSUCCINIC ACIDURIA

- **Autosomal recessive** disorder of amino acid metabolism
- 1:70,000 live births in the US
- **Enzyme Defect:** Argininosuccinate lyase – ASL (chromosome 7)
- **FL State Newborn Screen** YES
- **Clinical Presentation:** lethargy, poor appetite, vomiting, seizures, abnormal movements, difficulty breathing (tachypnea), irritability, hepatomegaly. **Trichorrhexis nodosa**
  - **Infantile:** 24-72 hours after birth
  - **Childhood:** Late infancy or early childhood
- **Lab Findings:** ↑↑ammonia, ↓arginine, ↑ citrulline↑ urine orotic acid
- **Diagnostic Test**
  - Ammonia and plasma and urinary organic acids
- **Treatment:** Protein restricted diet. Arginine supplementation
  - **Medication to treat NH_4^+:** sodium benzoate (not FDA approved), sodium phenylbutyrate (FDA approved 1996), and glycerol triphenylbutyrate (FDA approved 2013).
- **Long term Prognosis:** Neurocognitive deficiencies, behavior issues such as ADHD, developmental disability and seizures



ARGININEMIA

- **Autosomal recessive** disorder of arginine metabolism and removal of ammonia
- 1/300,000 to 1 million individuals
- **FL State Newborn Screen** NO
- **Enzyme Defect:** Arginase deficiency
- **Clinical Presentation:** Presents by 3 years of age
  - Lower extremity spasticity, failure to thrive, developmental delay and eventual loss of developmental milestones, intellectual disability, seizures, tremor, ataxia.
- **Diagnostic Test**
  - Ammonia
- **Treatment:** Low protein diet
- **Long term Prognosis:** With prompt and lifelong treatment, children with arginase deficiency may be able to live healthy lives with typical growth and learning.
- Even with treatment, some children still have effects from high blood levels of arginine and ammonia. This can result permanent learning problems, intellectual disability or spasticity.

A CASE TO REMEMBER

A neonate suspected of having a urea cycle defect after presenting with hyperammonemia, a primary respiratory alkalosis and a normal serum glucose. The infants' serum amino acids and urine organic acids are measured. **The infant has elevated serum glutamine and alanine amounts with low serum citrulline and arginine. The infant's urine orotic acid concentrations are low.**

Of the following, the most likely enzyme that is deficient in the infant in this vignette is:

A. Arginase
B. Argininosuccinic acid synthetase
C. Ornithine carbamyl transferase
D. Carbamyl phosphate synthetase
E. N-acetylglutamate syntetase

INBORN ERRORS OF METABOLISM

QUICK FACTS

- Individually rare. However, accounts for **20% of diagnosis in sick full term infants**
- Non-specific presenting symptoms
  - Requires high index of suspicion
- Many are treatable with early recognition
- Common in certain populations
- Detailed knowledge of biochemical pathways is NOT necessary to treat patients during the initial evaluation
- Important to known which IEMs are tested on the newborn screen in your state
- **Emergent management:** Stop oral feeds, provide D10 (GIR 8-10), correct acidosis, treat severe hyperammonemia. Send initial screening labs: ABG, lactate, glucose, electrolytes, liver function (attn: bilirubin), CBC with diff. **Consult Genetics.**
- Even in cases of early neonatal death, diagnosis is important for family planning.

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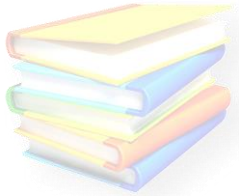

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Gustavo H.B. Maegawa MD, PhD

Jim Wynn, MD

Irina Prelipcean, MD

Drug or Chemical	Disorder	Mechanism of Action
Arginine	Selected urea-cycle disorders	Replenishes stores
Betaine	Homocystinuria	Removes substrate
Biotin	Carboxylase deficiencies	Serves as cofactor for pathways
Carnitine	Carnitine deficiency	Replenishes stores
Cholesterol	Smith-Lemli-Opitz syndrome	Replenishes stores
Citrulline	Selected urea-cycle disorders	Replenishes stores
Cysteamine	Cystinosis	Removes substrate
Cystine	Homocystinuria	Replenishes stores
Dichloroacetate	Primary lactic acidosis	Stimulates enzyme
Folic acid	Homocystinuria	Serves as cofactor for pathways
Imiglucerase	Gaucher's disease	Replaces enzyme
Metronidazole	Propionic and methylmalonic aciduria	Reduces propionate absorption
NTBC[a]	Tyrosinemia	Blocks enzyme
Pyridoxine	Homocystinuria	Serves as cofactor for pathways
Riboflavin	Glutaric acidemias	Serves as cofactor for pathways
Sodium benzoate	Urea-cycle disorders	Removes substrate
Sodium phenylbutyrate	Urea-cycle disorders	Removes substrate
Ubiquinone[b]	Mitochondrial problems	Serves as cofactor for substrate

[a]NTBC = 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione.
[b]Also known as coenzyme Q_.