Ann & Robert H. Lurie Children's Hospital of Chicago®

A Specialized Case-Based Review in Newborn Screening of Inborn Errors of Metabolism – An Approach to Diagnosis and Management

Joshua Baker, DO, FACMGG

Director of Inborn Errors of Metabolism
Director of Newborn Screening Program
Division of Genetics, Genomics, and Metabolism
Ann & Robert H. Lurie Children's Hospital of Chicago
Assistant Professor of Pediatrics
Northwestern University, Feinberg School of Medicine

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT RANKED IN 10 SPECIALTIES 2021-22

MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER

Ann & Robert H. Lurie Children's Hospital of Chicago®

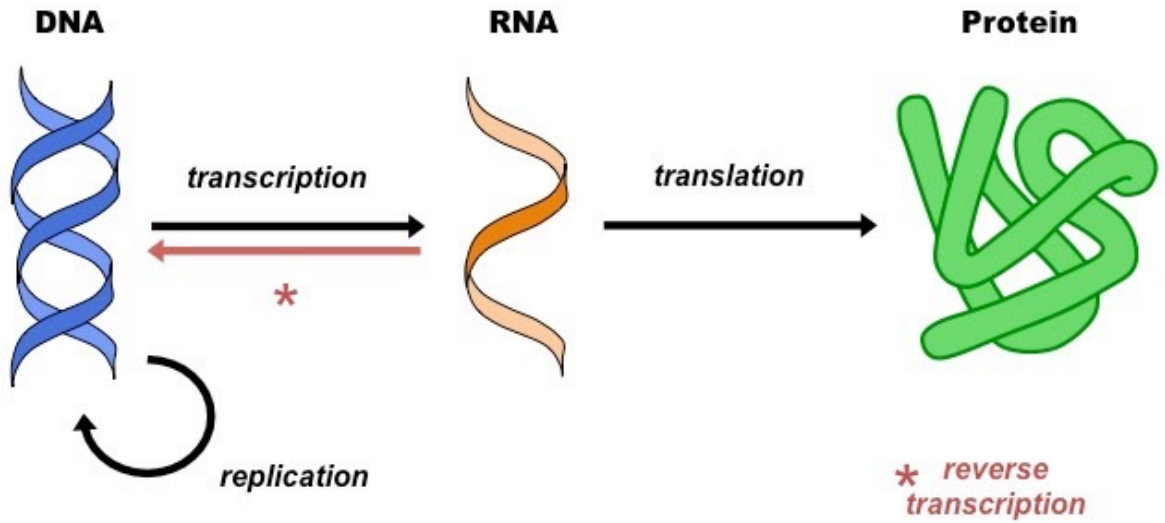
Objectives

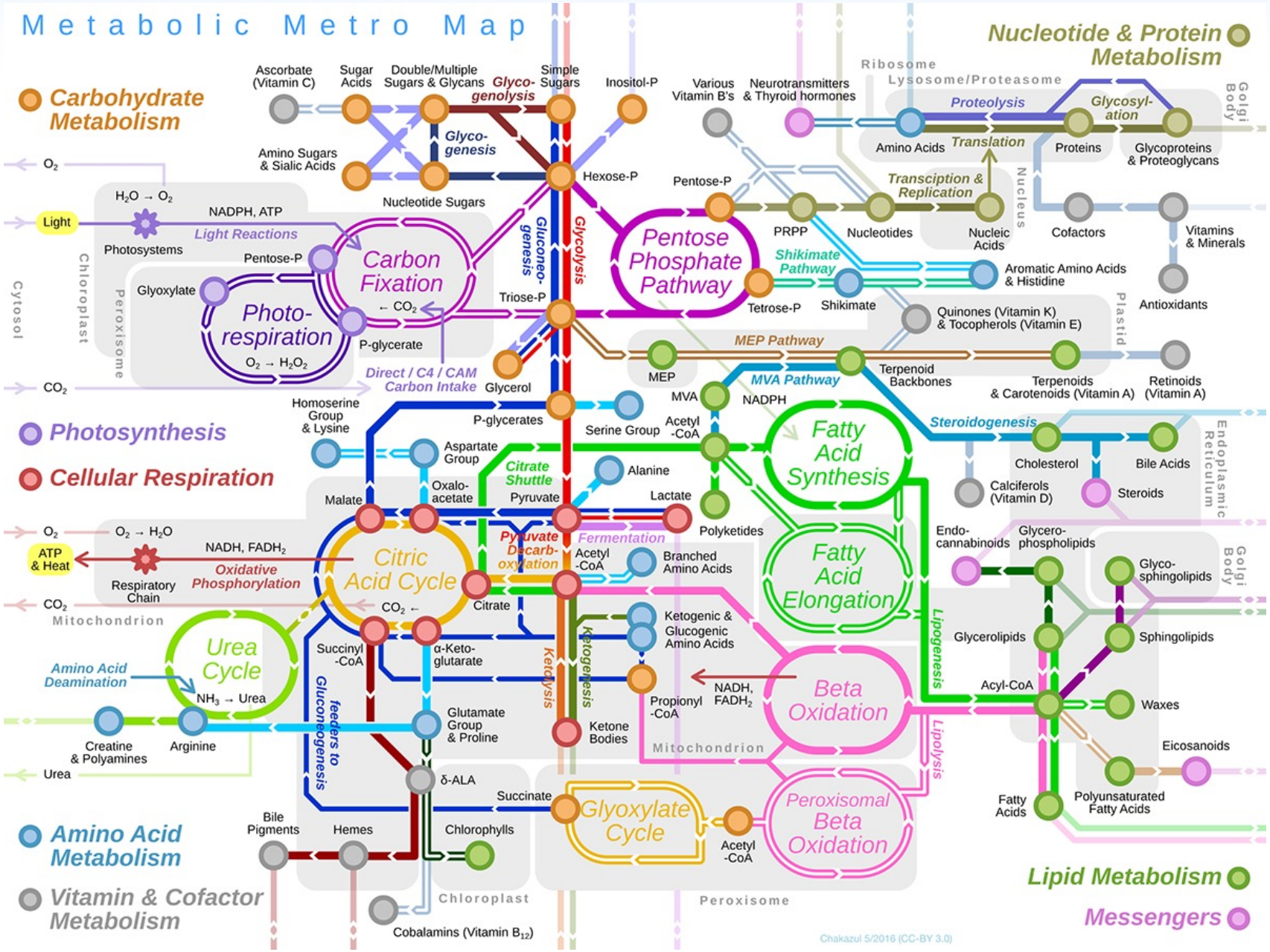
- Analyze the different categories of metabolic disease and describe classical clinical findings for each group.
- Review the approach to metabolic disease evaluation.
- Evaluate newborn screen results for emergent metabolic evaluations.

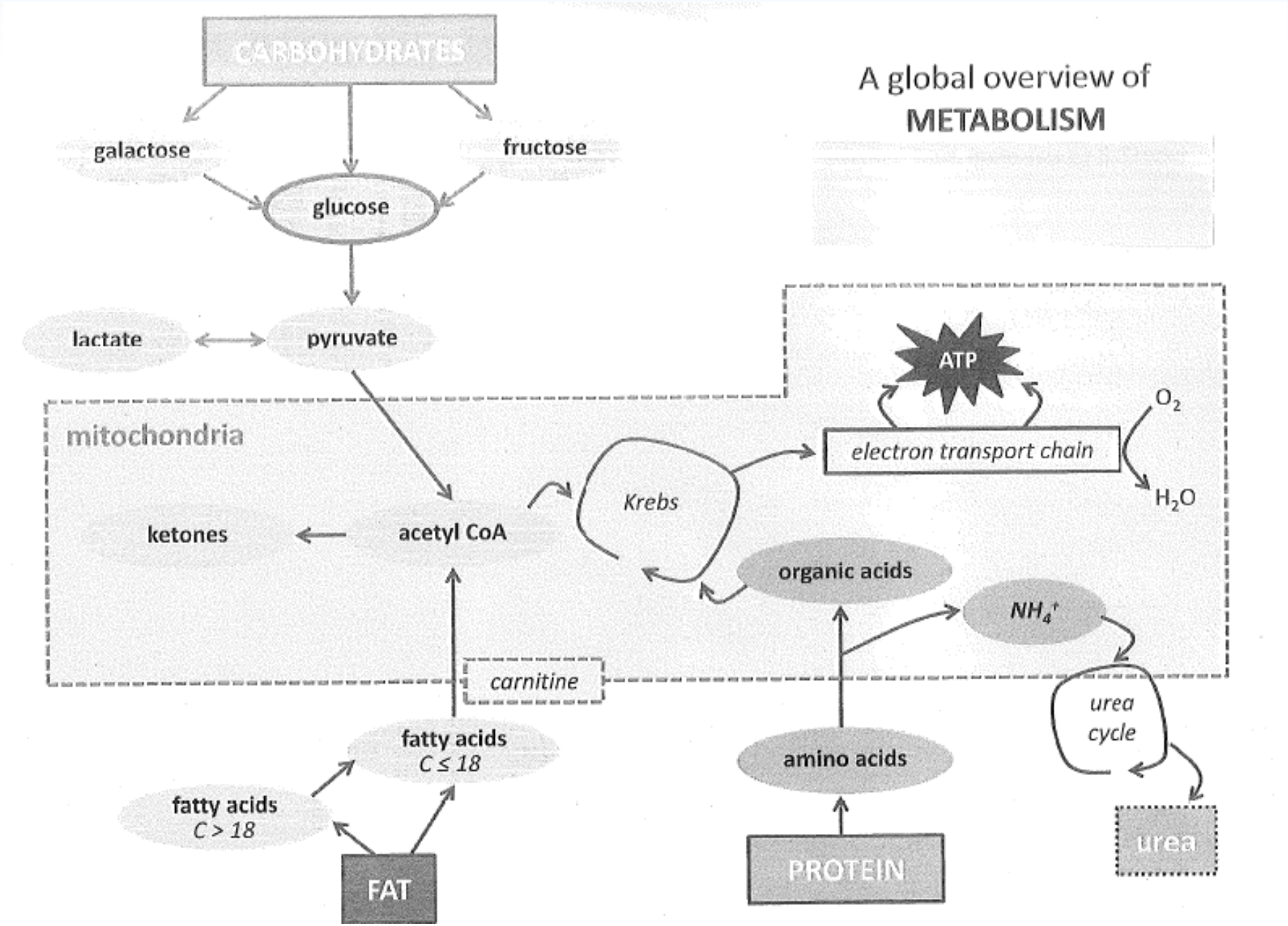
Ann & Robert H. Lurie
Children's Hospital of Chicago®

Intro to Metabolism

Central Dogma




Metabolic Metro Map
Carbohydrate Metabolism
Photosynthesis
Cellular Respiration
Amino Acid Metabolism
Vitamin & Cofactor Metabolism
Nucleotide & Protein Metabolism
Lipid Metabolism
Messengers
Ascorbate (Vitamin C)
Sugar Acids
Double/Multiple Sugars & Glycans
Glyco-genolysis
Simple Sugars
Inositol-P
Amino Sugars & Sialic Acids
Glyco-genesis
Nucleotide Sugars
Hexose-P
Pentose-P
Various Vitamin B's
Neurotransmitters & Thyroid hormones
Ribosome
Lysosome/Proteasome
Proteolysis
Glycosyl-ation
Golgi Body
Amino Acids
Translation
Proteins
Glycoproteins & Proteoglycans
Transciption & Replication
Nucleus
PRPP
Nucleotides
Nucleic Acids
Cofactors
Vitamins & Minerals
Shikimate Pathway
Aromatic Amino Acids & Histidine
Tetrose-P
Shikimate
Quinones (Vitamin K) & Tocopherols (Vitamin E)
Antioxidants
Plastid
MEP Pathway
MEP
Terpenoid Backbones
Terpenoids & Carotenoids (Vitamin A)
Retinoids (Vitamin A)
MVA Pathway
MVA
NADPH
Steroidogenesis
Cholesterol
Bile Acids
Calciferols (Vitamin D)
Steroids
Endoplasmic Reticulum
Endo-cannabinoids
Glycero-phospholipids
Glyco-sphingolipids
Glycerolipids
Sphingolipids
Acyl-CoA
Waxes
Eicosanoids
Polyunsaturated Fatty Acids
Fatty Acids
Lipogenesis
Lipolysis
Fatty Acid Synthesis
Fatty Acid Elongation
Beta Oxidation
Peroxisomal Beta Oxidation
Peroxisome
Mitochondrion
Chloroplast
Cytosol
Light
Photosystems
Light Reactions
NADPH, ATP
$H_2O \rightarrow O_2$
O_2
CO_2
Carbon Fixation
$\leftarrow CO_2$
Photo-respiration
$O_2 \rightarrow H_2O_2$
Glyoxylate
Peroxisome
Pentose-P
P-glycerate
Triose-P
Glycolysis
Gluconeo-genesis
Glycerol
Direct / C4 / CAM Carbon Intake
Pentose Phosphate Pathway
Homoserine Group & Lysine
P-glycerates
Serine Group
Aspartate Group
Oxalo-acetate
Citrate Shuttle
Alanine
Malate
Pyruvate
Lactate
Acetyl -CoA
Polyketides
Pyruvate Decarb-oxylation
Fermentation
Branched Amino Acids
ATP & Heat
Respiratory Chain
$O_2 \rightarrow H_2O$
NADH, $FADH_2$
Oxidative Phosphorylation
Citric Acid Cycle
$CO_2 \leftarrow$
Citrate
Ketogenic & Glucogenic Amino Acids
Succinyl -CoA
α-Keto-glutarate
Ketolysis
Ketogenesis
Ketone Bodies
Propionyl -CoA
NADH, $FADH_2$
Amino Acid Deamination
Urea Cycle
$NH_3 \rightarrow$ Urea
Creatine & Polyamines
Arginine
Urea
Glutamate Group & Proline
feeders to Gluconeogenesis
δ-ALA
Succinate
Glyoxylate Cycle
Acetyl -CoA
Bile Pigments
Hemes
Chlorophylls
Cobalamins (Vitamin B_{12})
Chakazul 5/2016 (CC-BY 3.0)


A global overview of
METABOLISM
CARBOHYDRATES
galactose
fructose
glucose
lactate
pyruvate
mitochondria
ATP
O_2
electron transport chain
H_2O
Krebs
ketones
acetyl CoA
organic acids
NH_4^+
carnitine
urea cycle
fatty acids
C ≤ 18
fatty acids
C > 18
amino acids
FAT
PROTEIN
urea

Ann & Robert H. Lurie Children's Hospital of Chicago®

When to suspect an IEM

- Abnormal newborn screening result
- Difficulty feeding, FTT
- Developmental delay, regression
- FHx: SIDS, early and/or sudden death, consanguinity
- Multiple organ systems involved: seizures, hyper/hypotonia, recurrent URI, valvular disease

Ann & Robert H. Lurie
Children's Hospital of Chicago®

Case Based Presentations

Ann & Robert H. Lurie
Children's Hospital of Chicago®

Case #1

Case #1 Presentation

- Newborn term breast-fed female
- Birth at 39 6/7; G1P0>1
- Uneventful prenatal care
- Poor feeding, progressive lethargy
- PCP called to say concern on “PKU” test and head to ED immediately

- Tonic spasms
- Abnormal movements
- Abnormal sweet smell to baby per mother

Ann & Robert H. Lurie Children's Hospital of Chicago®

Case Presentation – Physical Exam

Case Presentation

What labs do you want to obtain?

Lab Evaluation

- Glucose
  - 50 mg/dL
- Electrolytes
  - Na 130
  - K 4.8
  - Bicarb 13
- CBC:
  - Normal
- Lactate
  - 4.3 mol/L
- Venous Blood Gas
  - pH 7.2
- Ammonia
  - 88 µmol/L
- LFTs
  - AST 50 U/L
  - ALT 45 U/L
- Urinalysis
  - Large ketones

Ann & Robert H. Lurie
Children's Hospital of Chicago®

Organic Acidemias

Ann & Robert H. Lurie
Children's Hospital of Chicago®

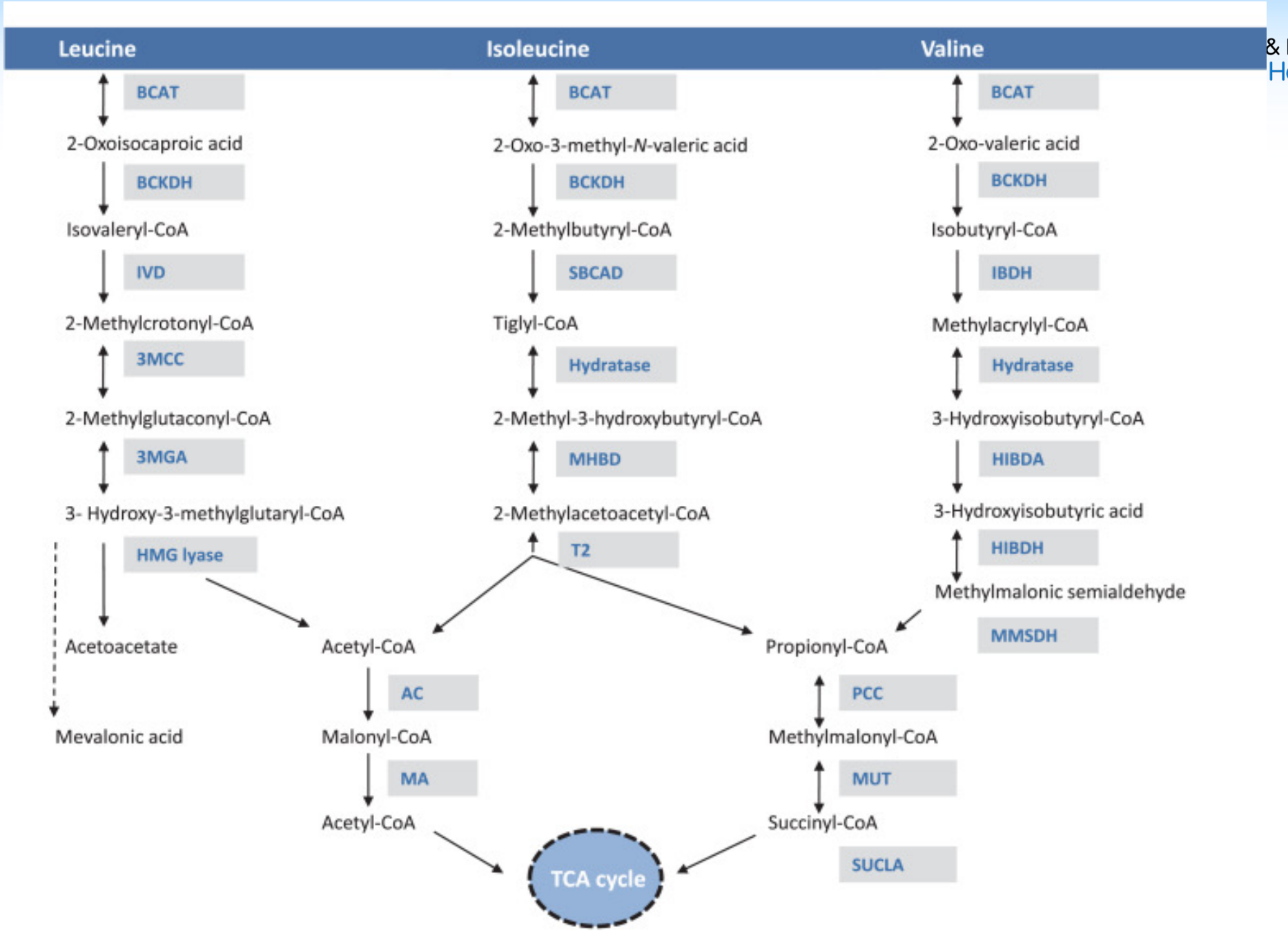
Maple Syrup Urine Disease (MSUD)

Ann & Robert H. Lurie Children's Hospital of Chicago®

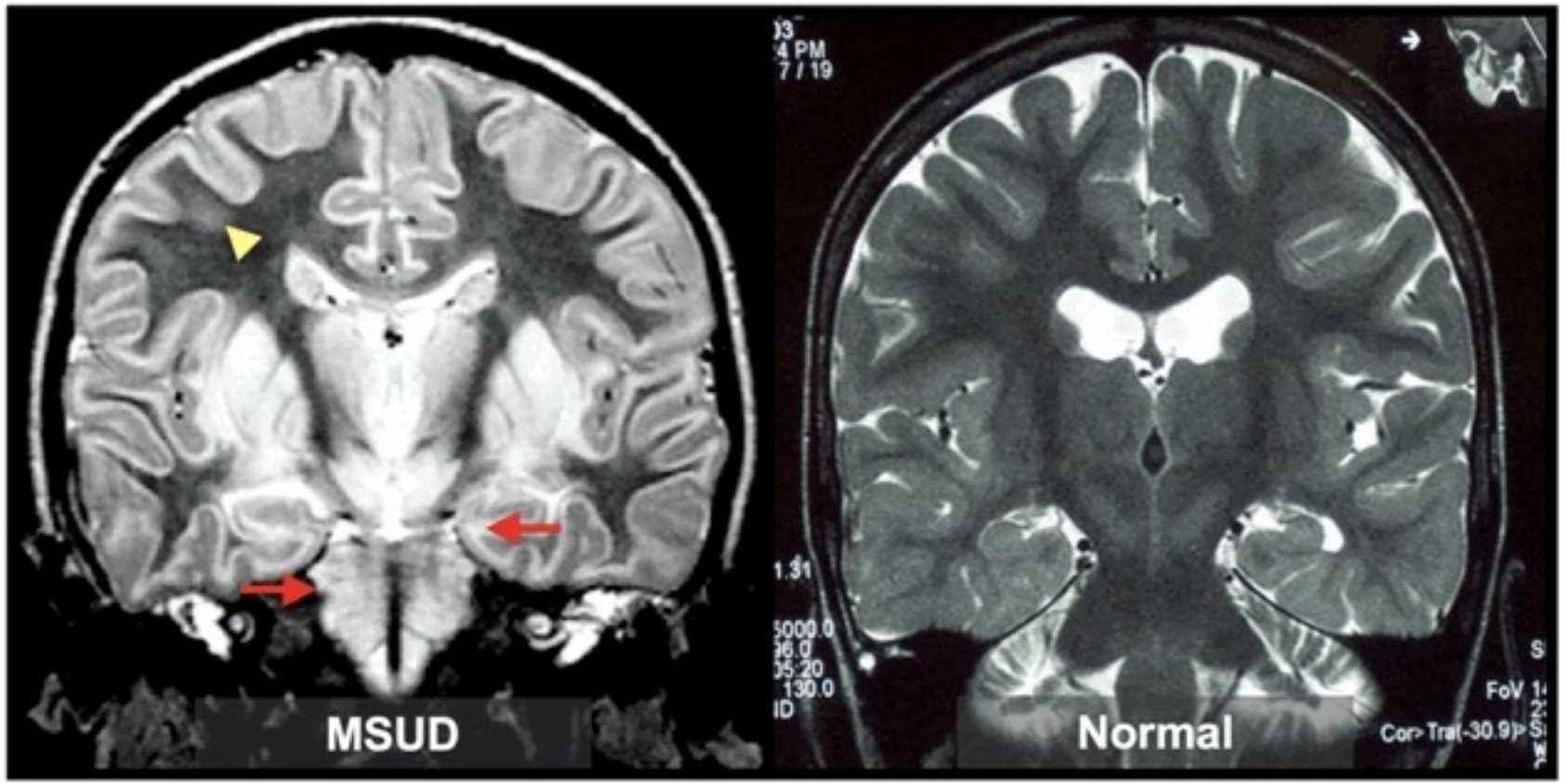
Maple Syrup Urine Disease

- Branched chain ketoacid dehydrogenase deficiency
- Autosomal recessive inheritance
- Incidence = 1/185,000 births
- 4 subunits – E1α, E1β, E2, and E3

- Severe neonatal form (<1% residual activity)
  - Few abnormalities on routine lab tests
  - Maple syrup odor
- Acute intermittent form (with residual activity)
- Thiamine Responsive


Leucine
Isoleucine
Valine
BCAT
2-Oxoisocaproic acid
BCKDH
Isovaleryl-CoA
IVD
2-Methylcrotonyl-CoA
3MCC
2-Methylglutaconyl-CoA
3MGA
3- Hydroxy-3-methylglutaryl-CoA
HMG lyase
Acetoacetate
Mevalonic acid
BCAT
2-Oxo-3-methyl-N-valeric acid
BCKDH
2-Methylbutyryl-CoA
SBCAD
Tiglyl-CoA
Hydratase
2-Methyl-3-hydroxybutyryl-CoA
MHBD
2-Methylacetoacetyl-CoA
T2
BCAT
2-Oxo-valeric acid
BCKDH
Isobutyryl-CoA
IBDH
Methylacrylyl-CoA
Hydratase
3-Hydroxyisobutyryl-CoA
HIBDA
3-Hydroxyisobutyric acid
HIBDH
Methylmalonic semialdehyde
MMSDH
Acetyl-CoA
AC
Malonyl-CoA
MA
Acetyl-CoA
Propionyl-CoA
PCC
Methylmalonyl-CoA
MUT
Succinyl-CoA
SUCLA
TCA cycle

Pathogenesis



Treatment

Acute

- Eliminate dietary protein intake
- Supplement valine and isoleucine
- Provide adequate non-protein energy
- Avoid hypotonic fluids
- Treat cerebral edema
  - As soon as symptoms develop
- Dialysis

Chronic

- Natural protein-restricted diet
- Supplement BCFAA medical foods
- Leucine intake in severe neonatal forms:
  - About 400–600 mg/day during childhood
  - After adolescence, 600–800 mg/day
- Supplement valine and isoleucine
- Thiamin supplementation
- Liver transplantation

Neurocognitive Outcomes and Quality of Life in Adults With Maple Syrup Urine Disease (MSUD)

ClinicalTrials.gov Identifier: NCT04828863

Recruitment Status : Recruiting
First Posted : April 2, 2021
Last Update Posted : October 5, 2022

See **Contacts and Locations**

View this study on Beta.ClinicalTrials.gov

Sponsor:

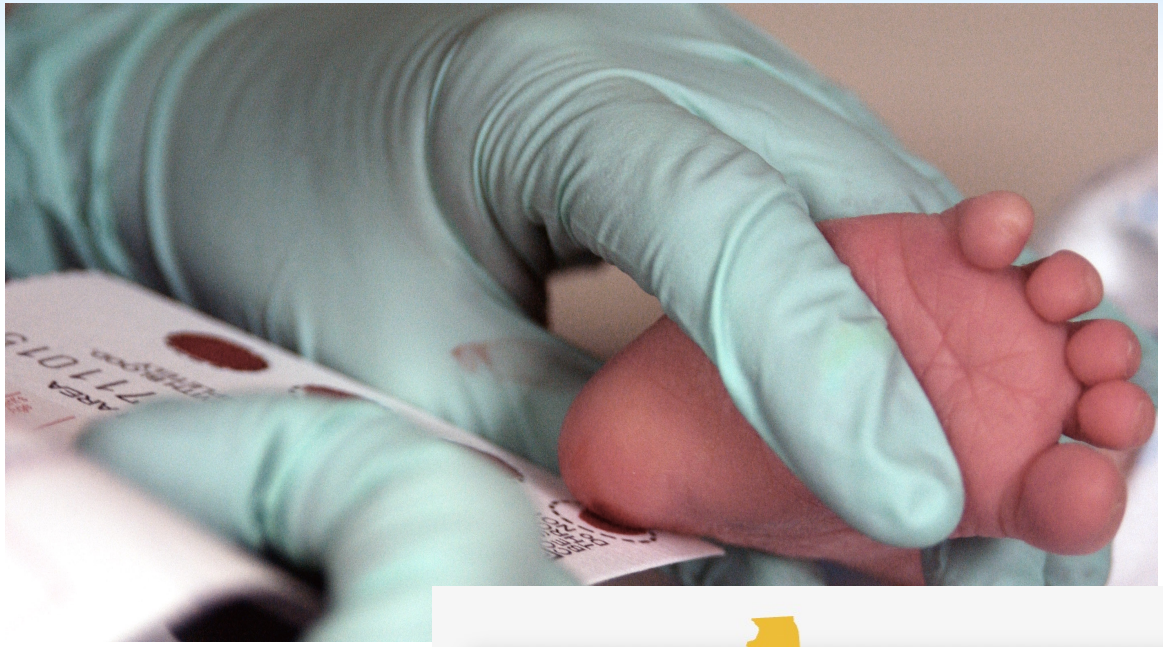
Children's Hospital of Philadelphia

Information provided by (Responsible Party):

Children's Hospital of Philadelphia

Ann & Robert H. Lurie
Children's Hospital of Chicago®

Newborn Screening



Ann & Robert H. Lurie Children's Hospital of Chicago®

baby's first test®

States

Illinois

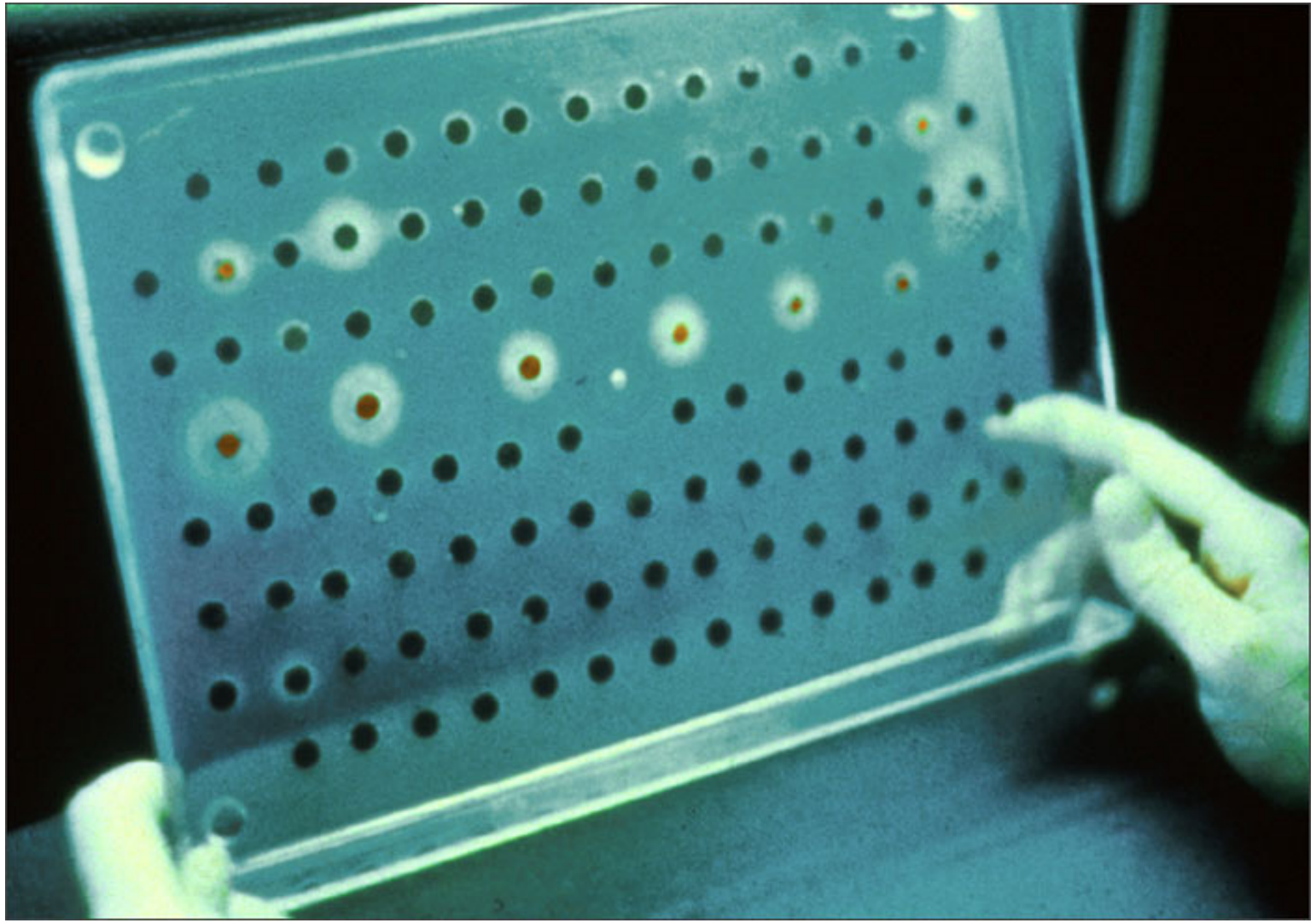
CONDITIONS SCREENED

Illinois currently screens for **65** conditions

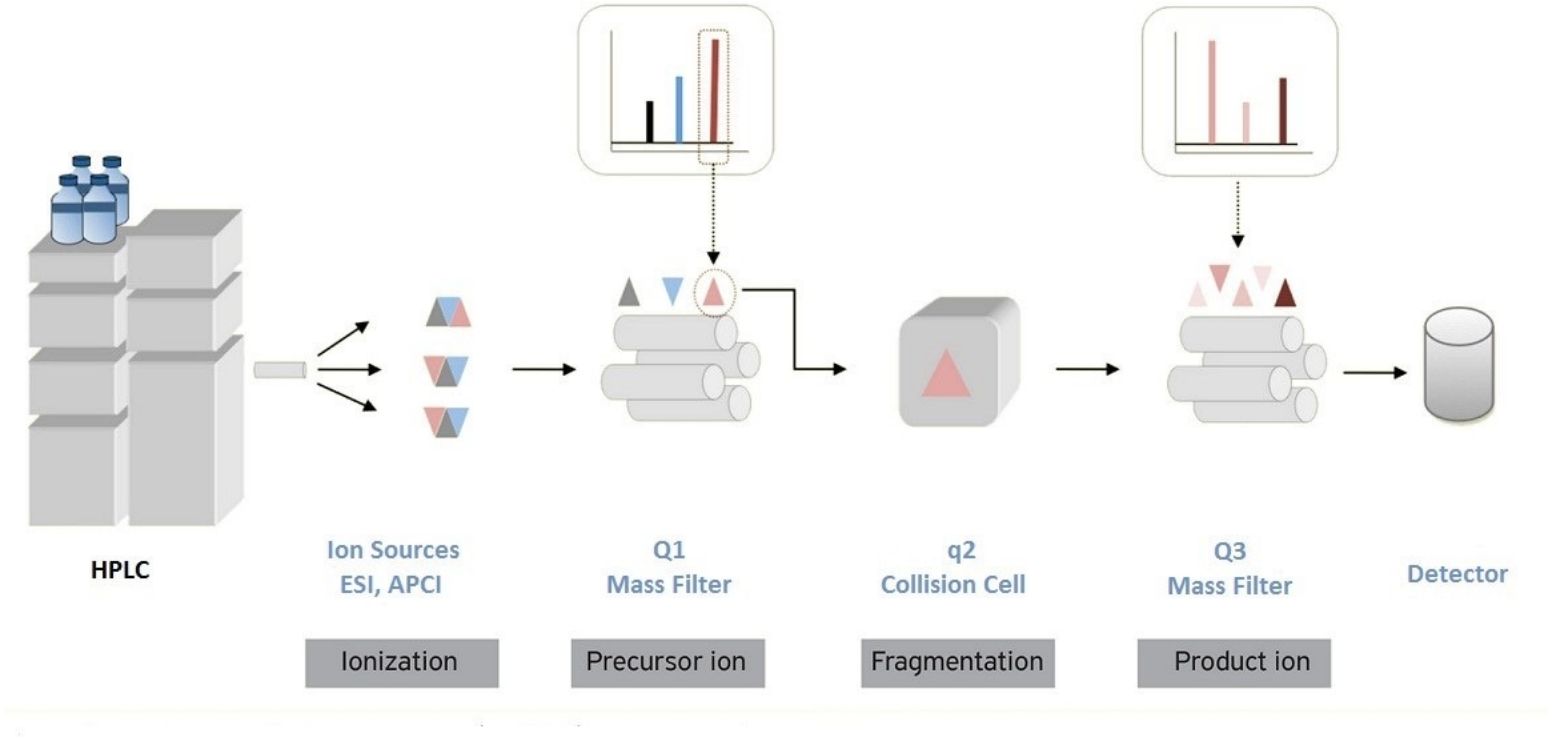
THE ILLINOIS PROGRAM

Each state runs its program differently, for more detailed information please visit their website here.

Guthrie Bacterial Inhibition Assay



Tandem Mass Spectrometry



Ann & Robert H. Lurie
Children's Hospital of Chicago®

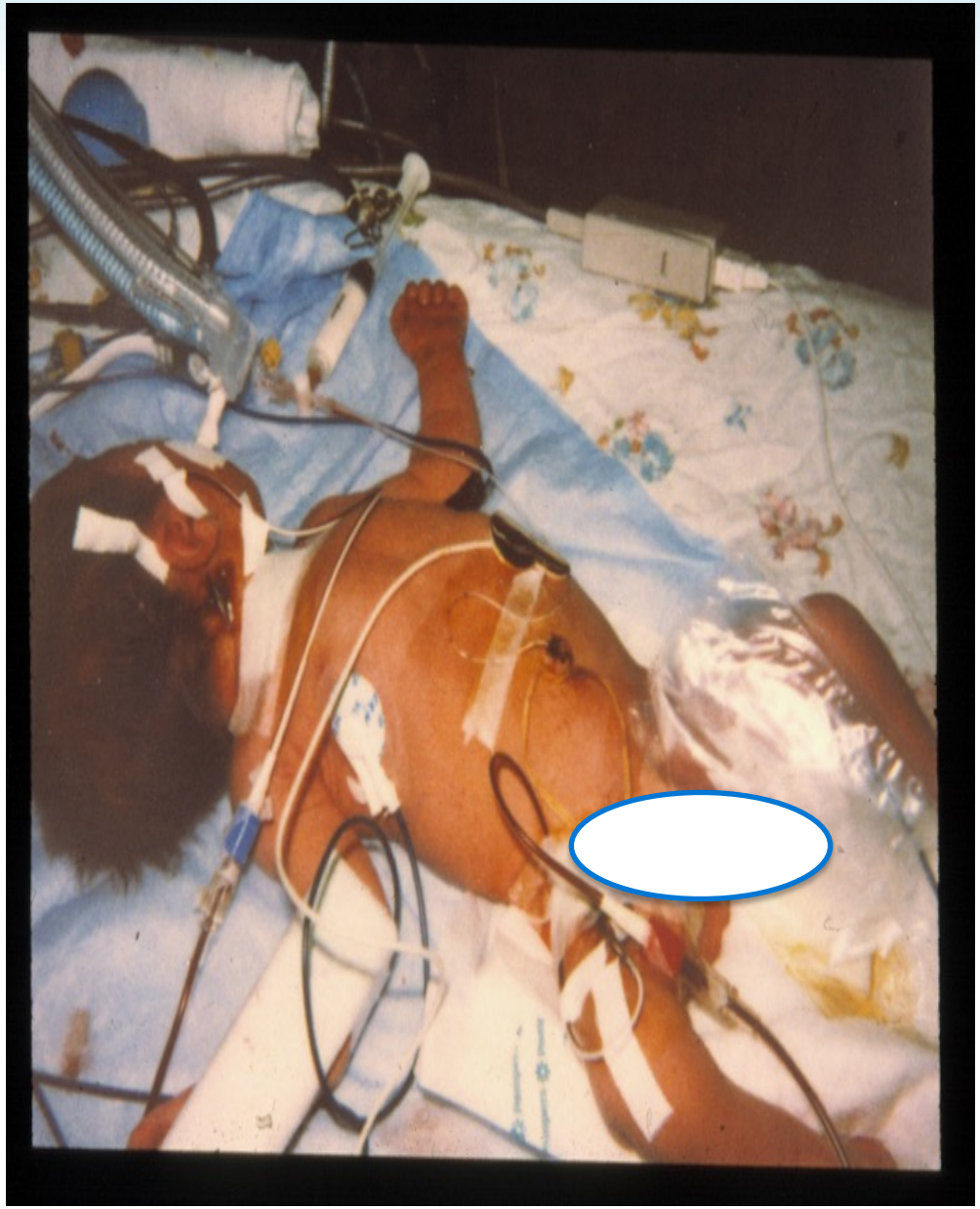
Case #2

Ann & Robert H. Lurie Children's Hospital of Chicago®

Case #2 Presentation

- Newborn Male Infant
- Delivered via SVD at 41 weeks to a 30 yo G3P1>2 Mother
- Apgars 8&9; No significant prenatal history
- DOL2 – Breast feeding with bottle supplementation; mother reports some spit ups and vomiting more than her previous pregnancy
- DOL3 – Infant appeared to have a seizure like episode, Transferred to OSH NICU. Admission notes state patient had low body temp and tachypnea. Septic work up initiated. NPO.
- DOL4 - Patient progressively more lethargic. Transferred to your NICU.

Physical Exam



Case Presentation

What labs do you want to obtain?

Ann & Robert H. Lurie Children's Hospital of Chicago®

Lab Evaluation

- Glucose
  - 80 mg/dL
- Electrolytes
  - Na 143
  - K 4.8
  - Cl 110
  - Bicarb 18
  - BUN 2
- CBC:
  - WBC 12,000
  - Plts 125,000
- Venous Blood Gas
  - pH 7.54
- Lactate
  - 3 mol/L
- Ammonia
  - 1260 µmol/L
- LFTs
  - AST 50 U/L
  - ALT 80 U/L
- Urinalysis
  - No ketones

Ann & Robert H. Lurie Children's Hospital of Chicago®

Case #2

- Head CT - Cerebral edema present; No bleeding seen

• Citrulline	5 µmol	(RR 10-20)
• Glutamine	1200 µmol	(RR 300-700)
• Arginine	4 µmol	(RR 10-130)

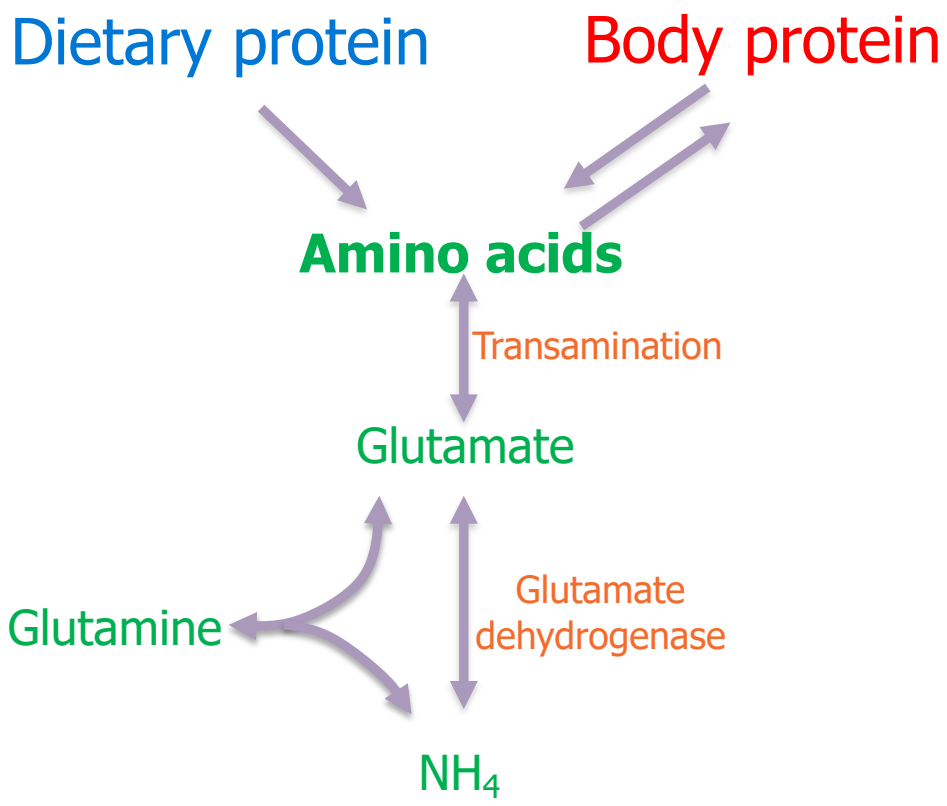
- Arginosuccinate – Not Detected

- What other test should be sent?

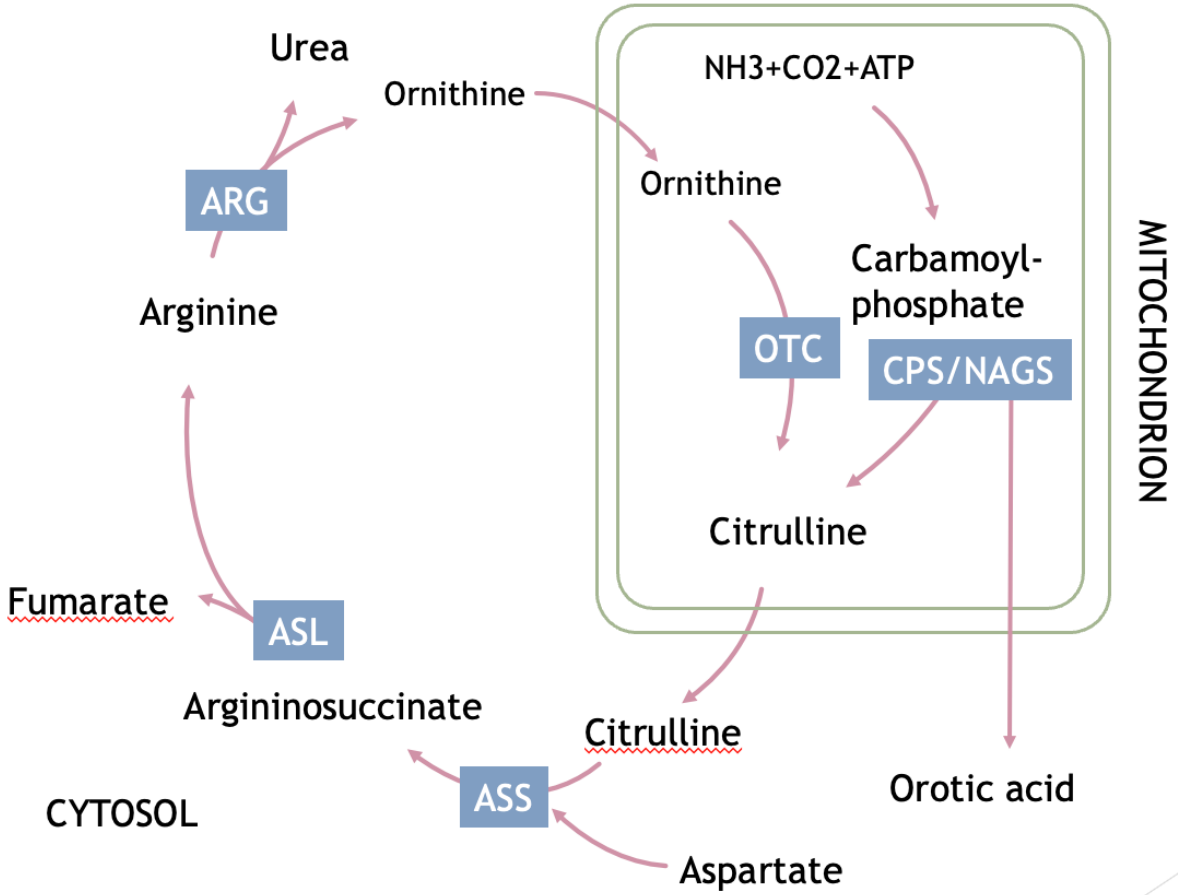
Ann & Robert H. Lurie
Children's Hospital of Chicago®

Urea Cycle Disorders

Amino Acid Balance



Urea Cycle


Urea
Ornithine
ARG
Arginine
NH3+CO2+ATP
Ornithine
Carbamoyl-
phosphate
OTC
CPS/NAGS
Citrulline
MITOCHONDRION
Fumarate
ASL
Argininosuccinate
Citrulline
Orotic acid
CYTOSOL
ASS
Aspartate

Ann & Robert H. Lurie Children's Hospital of Chicago®

Signs and Symptoms of Hyperammonemia

- Headache
- Personality and Behavioral changes
- Sleep disorders
- Anorexia
- Vomiting
- Confusion
- Psychomotor agitation
- Delusions
- Hallucinations
- Slurred speech

Ornithine Transcarbamylase Deficiency

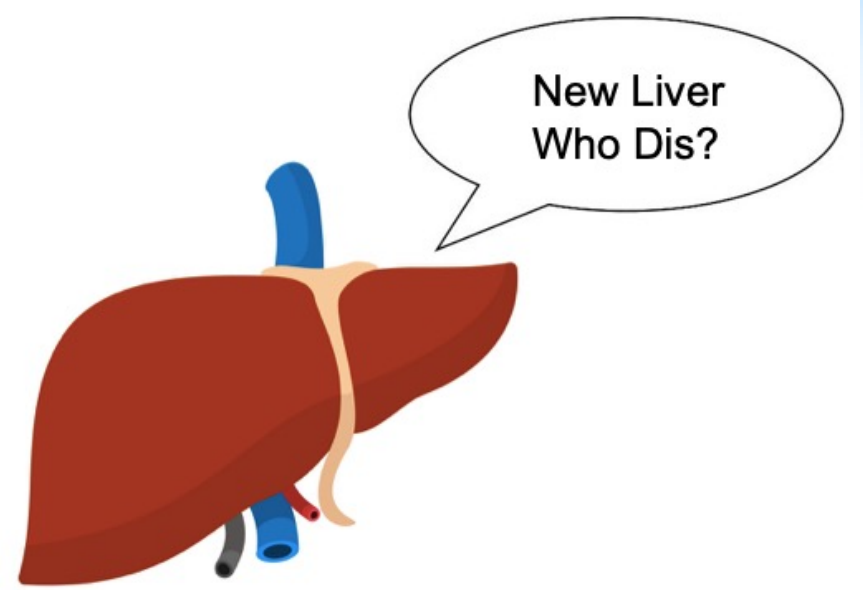
Enzyme defect: Ornithine Transcarbamylase (OTC)

Gene: *OTC* on chromosome Xp21.1

Frequency: 1/14,000

Inheritance: X-linked

Urea Cycle Disorders



Acute Symptoms
- Seizures, Coma, Brain Edema, Death

Long Term Symptoms
- Cognitive Impairment/Intellectual Disability, Spastic Quadriplegia, Ataxia

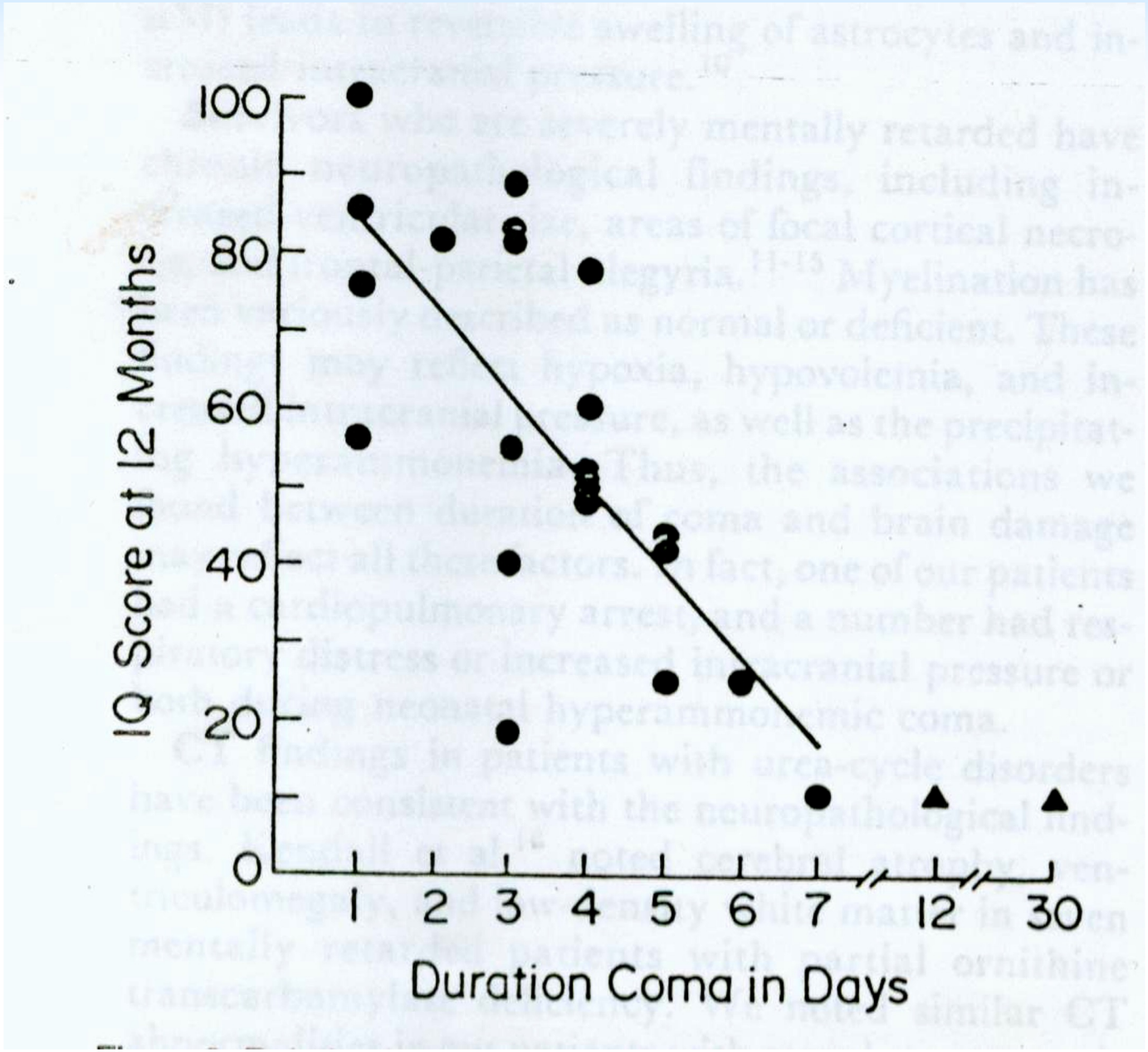
Treatment

<u>Crisis</u>

- No protein
- Dextrose Containing IVF + IL
- Sodium phenylacetate/Sodium benzoate + IV Arginine
- Dialysis

<u>Long Term</u>

- Protein Restricted Diet
- Ammonia Scavengers
- Liver Transplant
- Gene Therapy



Outcome Data in Early Series: Msall, et al, NEJM, 1984

Ann & Robert H. Lurie
Children's Hospital of Chicago®

Case #3

Case #3

- Neonate readmitted on DOL 3 of life with respiratory distress
- Birth Weight 2.2 kg –> Now 2.14 kg
- Exclusively breast feeding – now feeding poorly
- Fam Hx: Noncontributory
- PE:
  - Hypotonic
  - Increased respiratory rate – nasal flaring; retractions
  - Increased cap refill
  - Non-dysmorphic in appearance

Ann & Robert H. Lurie Children's Hospital of Chicago®

Case #3

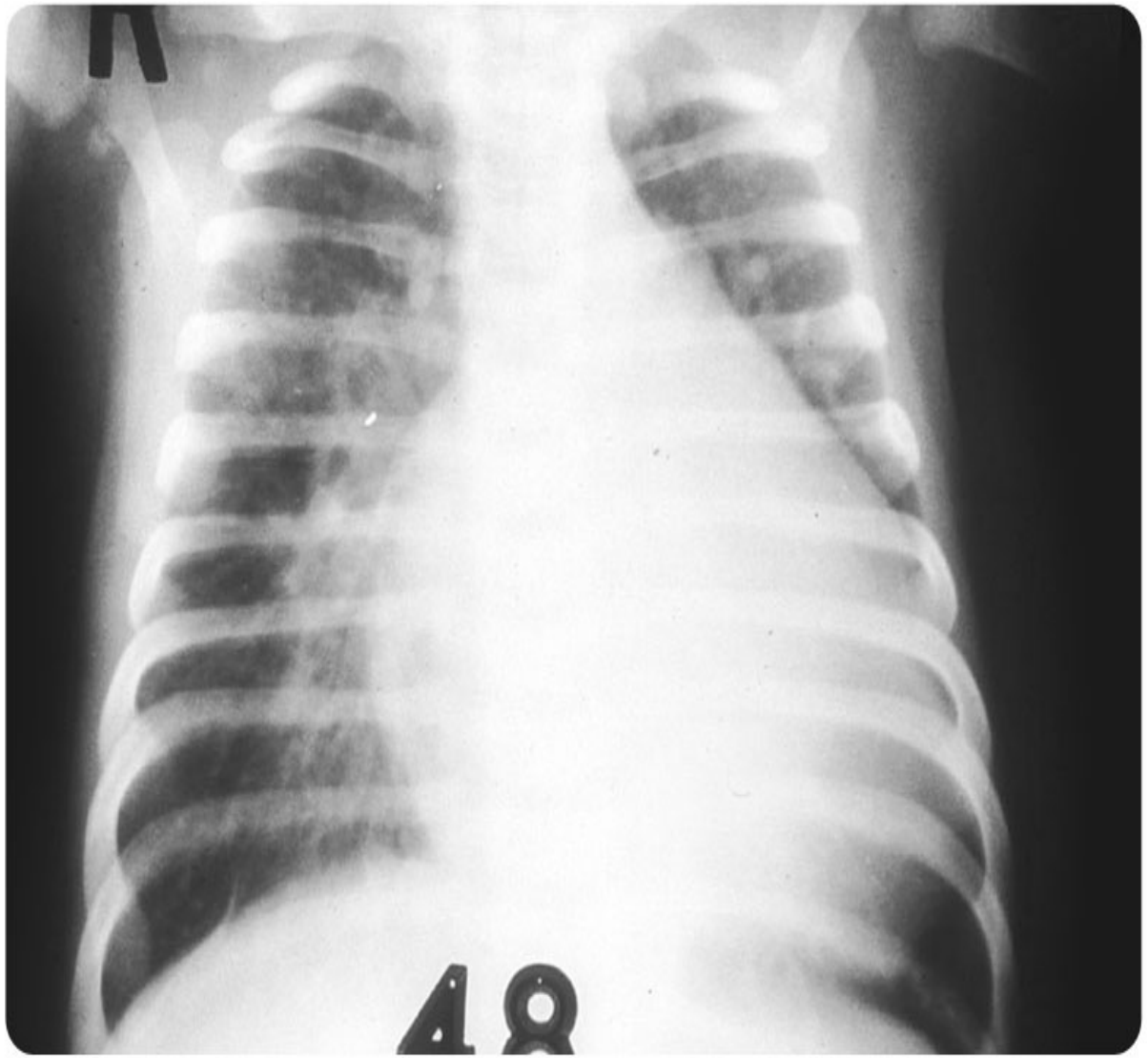
What labs should we want to obtain?

Ann & Robert H. Lurie Children's Hospital of Chicago®

Case #3 - Initial lab evaluation

- Glucose
  - 25 mg/dL (1.4 mmol/L)
- Venous Blood Gas
  - pH 7.2, bicarb 17, base excess -5, anion gap 12
- Lactate
  - 6.3 mol/L
- Ammonia
  - 120 µmol/L
- LFTs
  - AST 230 U/L (3.9 µkat/L)
  - ALT 200 (3.4 µkat/L)
- CPK
  - 500 U/L (8.5 µkat/L)
- Urinalysis, ketones
  - Trace ketones

Case #3 - Chest X-ray



Ann & Robert H. Lurie Children's Hospital of Chicago®

Case #3 - Echo

- Dilated cardiomyopathy identified on cardiac echo
- Ejection fraction 20%

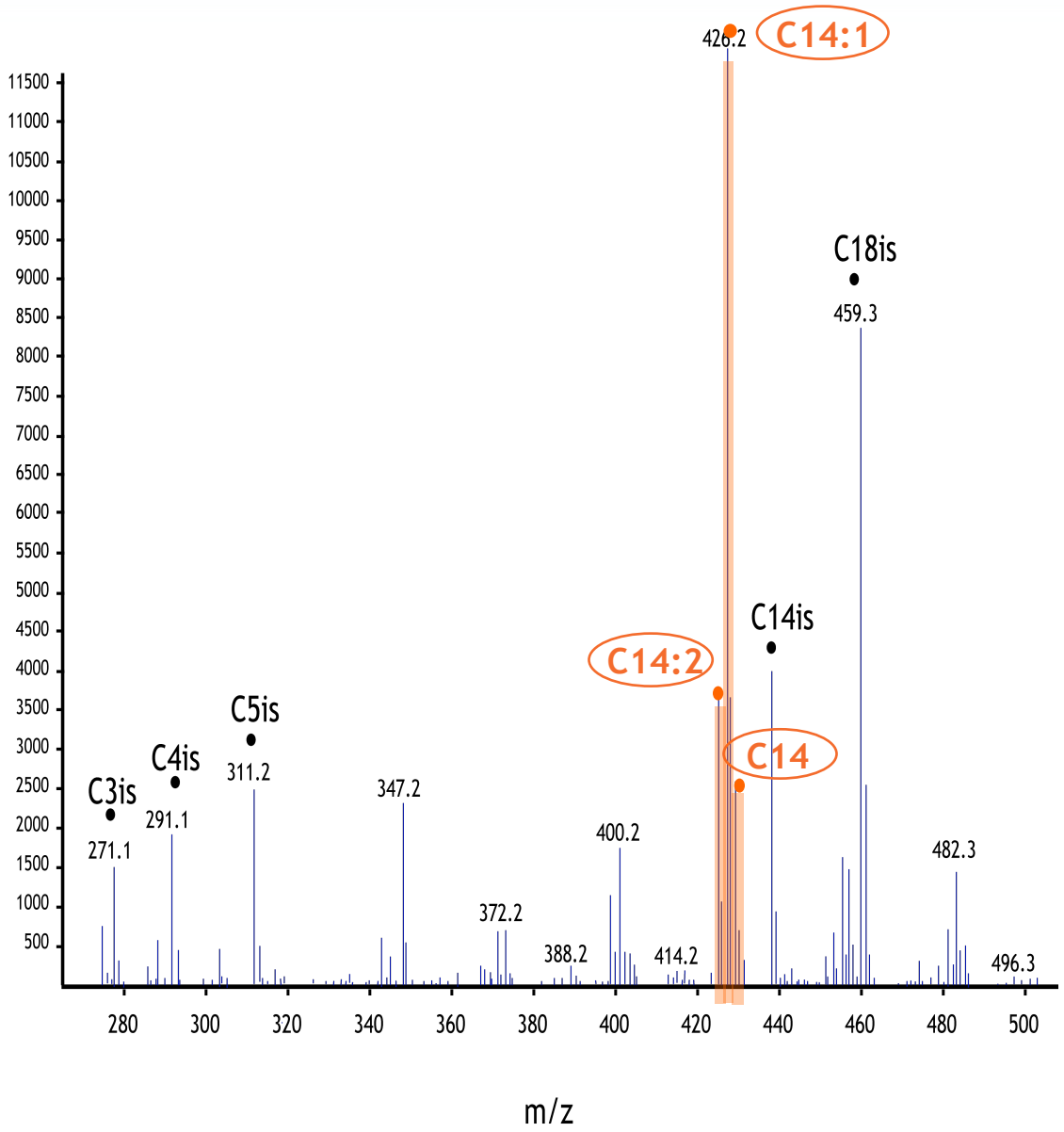
Ann & Robert H. Lurie Children's Hospital of Chicago®

Case #3 - Summary

- Neonate with dilated cardiomyopathy
- Hypoglycemia, mild hyperammonemia, and mild ketonuria
- Acidosis may be metabolic/secondary to cardiac failure

- What is the likely diagnosis?
- What do you want to do next?

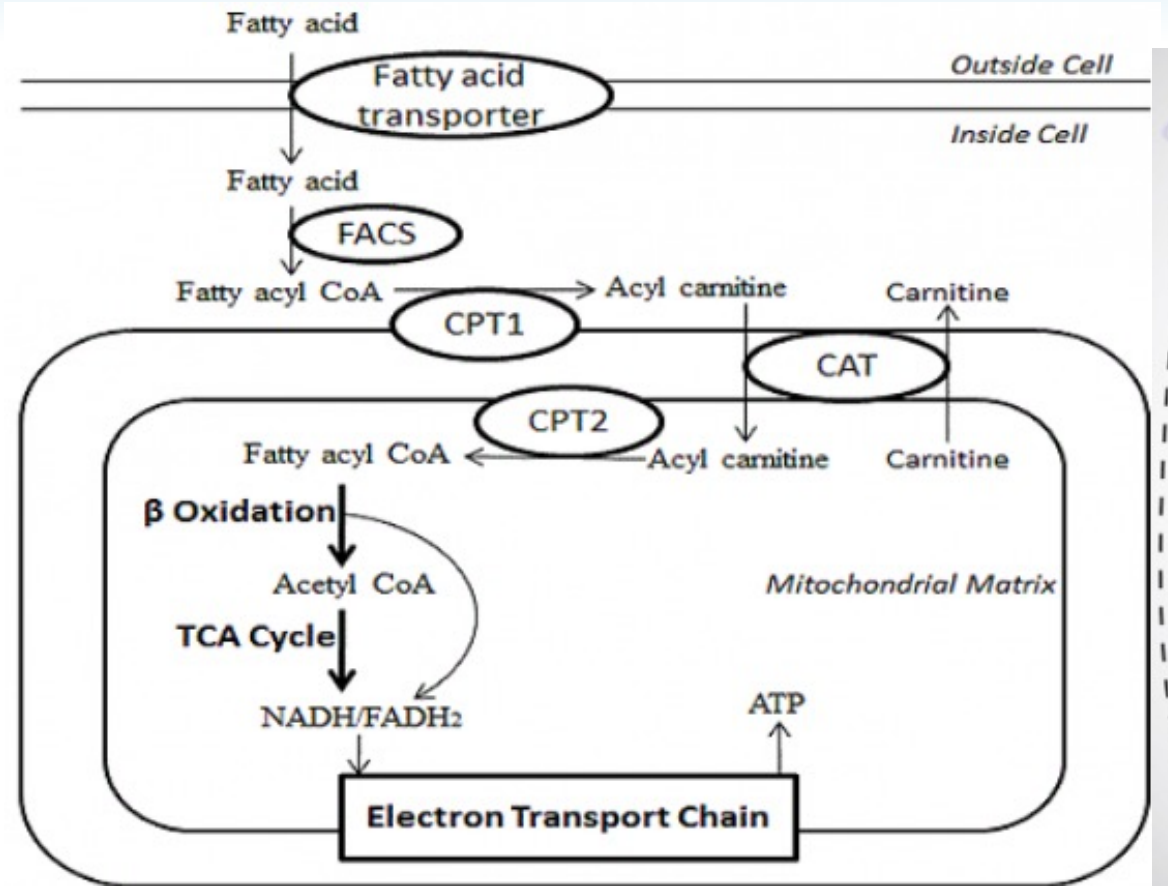
Case #3 - Acylcarnitine profile

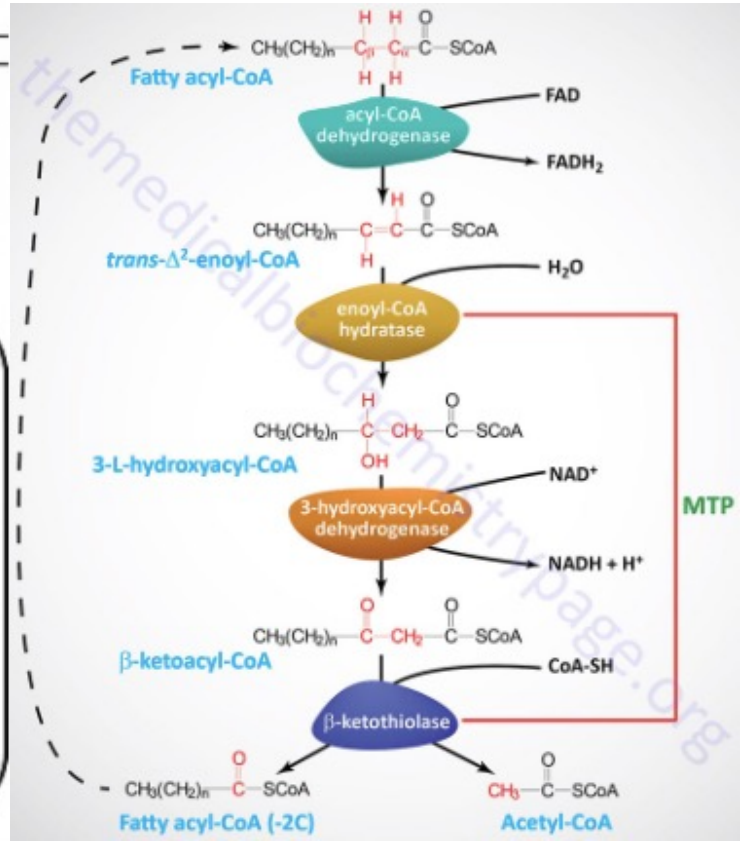


Ann & Robert H. Lurie Children's Hospital of Chicago®

Fatty Acid Oxidation Disorders


DOUBLE
McDonald's
Big Mac
PULL TO OPEN
McDonald's
Quarter Pounder
PULL TO OPEN
Quarter Pounder
Quarter Pounder
with cheese
PULL TO OPEN
Quarter Pounder
with cheese
DOUBLE
McDonald's





Natasha Fillmore, Osama Abo Alrob and Gary D. Lopaschuk. The authors are from Cardiovascular Research Centre, Mazankowski Alberta Heart Institute University of Alberta, Edmonton, Canada. DOI: 10.21748/lipidlibrary.39187
https://themedicalbiochemistrypage.org/lipolysis-and-the-oxidation-of-fatty-acids/

Very Long Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency

Ann & Robert H. Lurie Children's Hospital of Chicago®

Frequency: 1:63,481 (USA) (Relatively common fatty acid oxidation defect)

Cause: pathogenic variants in *ACADVL* gene; AR

Diagnosis: plasma acylcarnitine profile (elevated C14:1, normalize rapidly after stress), DNA testing (part of initial tests)

Therapy: Avoidance of fasting, prompt treatment of infection, MCT oil in patients with persistently abnormal acylcarnitines, low-fat diet, Essential FA, carnitine (25 mg/kg) with low plasma levels (unproven), MCT oil/sugary drinks with exercise.

Monitoring: AST, ALT, CK, carnitine F & T, Acylcarnitines, Heart Monitoring

Treatment & Management

- **Diet:** Avoidance of fasting
  - Infants: frequent feedings, initially every 3-4 hours
  - Low fat diet is controversial

- **Carnitine:**
  - Oral supplementation, 50-100 mg/kg/day
  - Correction of secondary carnitine deficiency
  - Controversial, as efficacy has not been proven

Ann & Robert H. Lurie Children's Hospital of Chicago®

Treatment & Management

- Any time the child is sick:
  - Contact metabolic physician
  - Evaluation: Prophylactic intravenous 10% glucose (WITH ELECTROLYTES) if child is unable to eat, vomiting or physiologically stressed
  - Threshold for aggressive treatment should be very low

Ann & Robert H. Lurie
Children's Hospital of Chicago®

Case #4

Case #4 – Presentation

- Neonate readmitted on DOL 3 of life with respiratory distress
- Birth Weight 2.2 kg –> Now 2.14 kg
- Exclusively breast feeding – now feeding poorly
- Fam Hx: Noncontributory
- PE:
  - Hypotonic (Severe)
  - Increased respiratory rate – nasal flaring; retractions
  - Increased cap refill
  - Non-dysmorphic in appearance

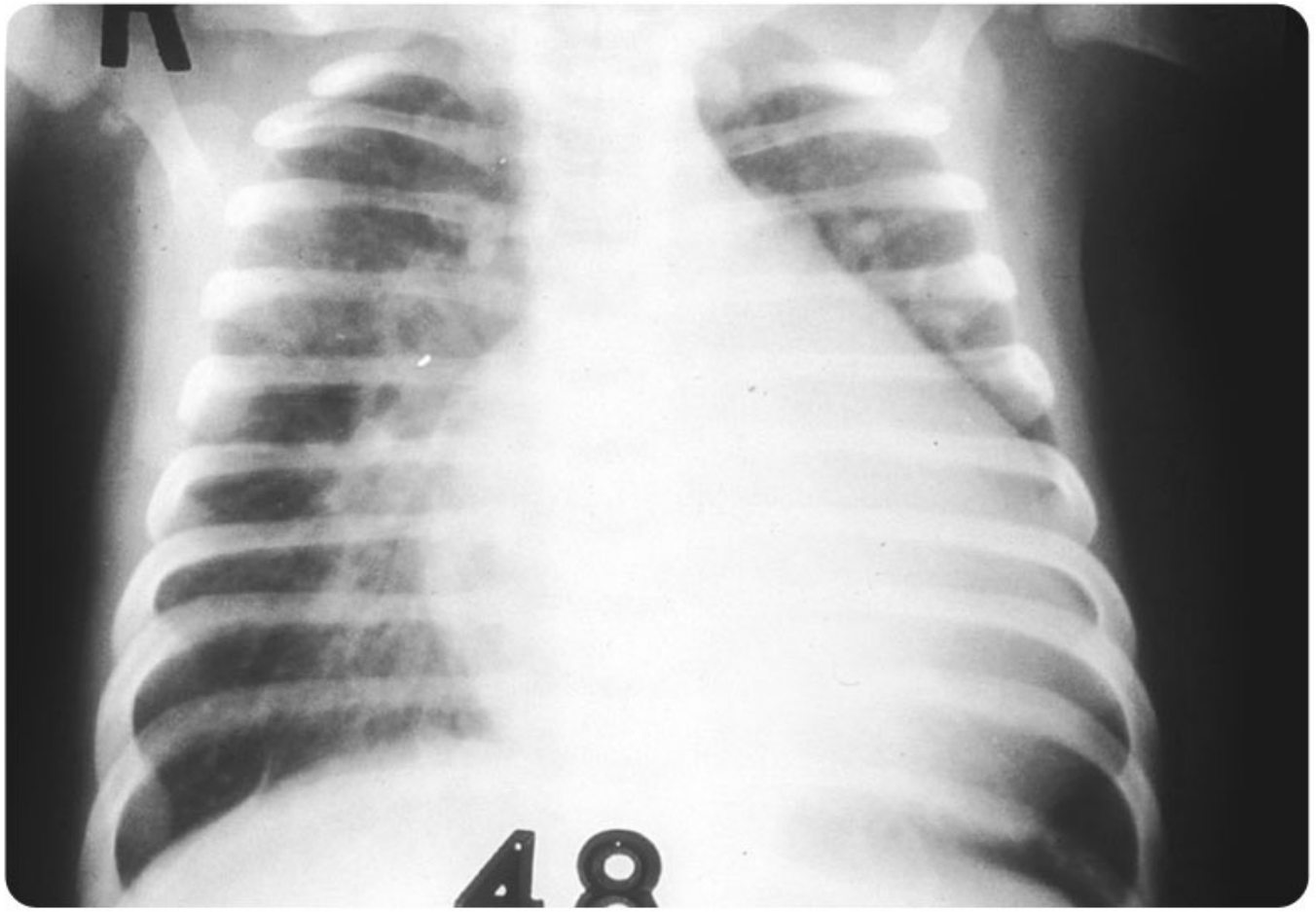
Case Presentation

What labs do you want to obtain?

Lab Evaluation

- Glucose
  - 70 mg/dL
- Electrolytes
  - Na 145
  - K 4.8
  - Bicarb 17
- CBC:
  - Normal
- Lactate
  - 6.3 mol/L
- Venous Blood Gas
  - pH 7.2
- Ammonia
  - 120 µmol/L
- LFTs
  - AST 50 U/L
  - ALT 80 U/L
- Urinalysis
  - No ketones
- CK
  - 1200 U/L

Case #4 - Chest X-ray



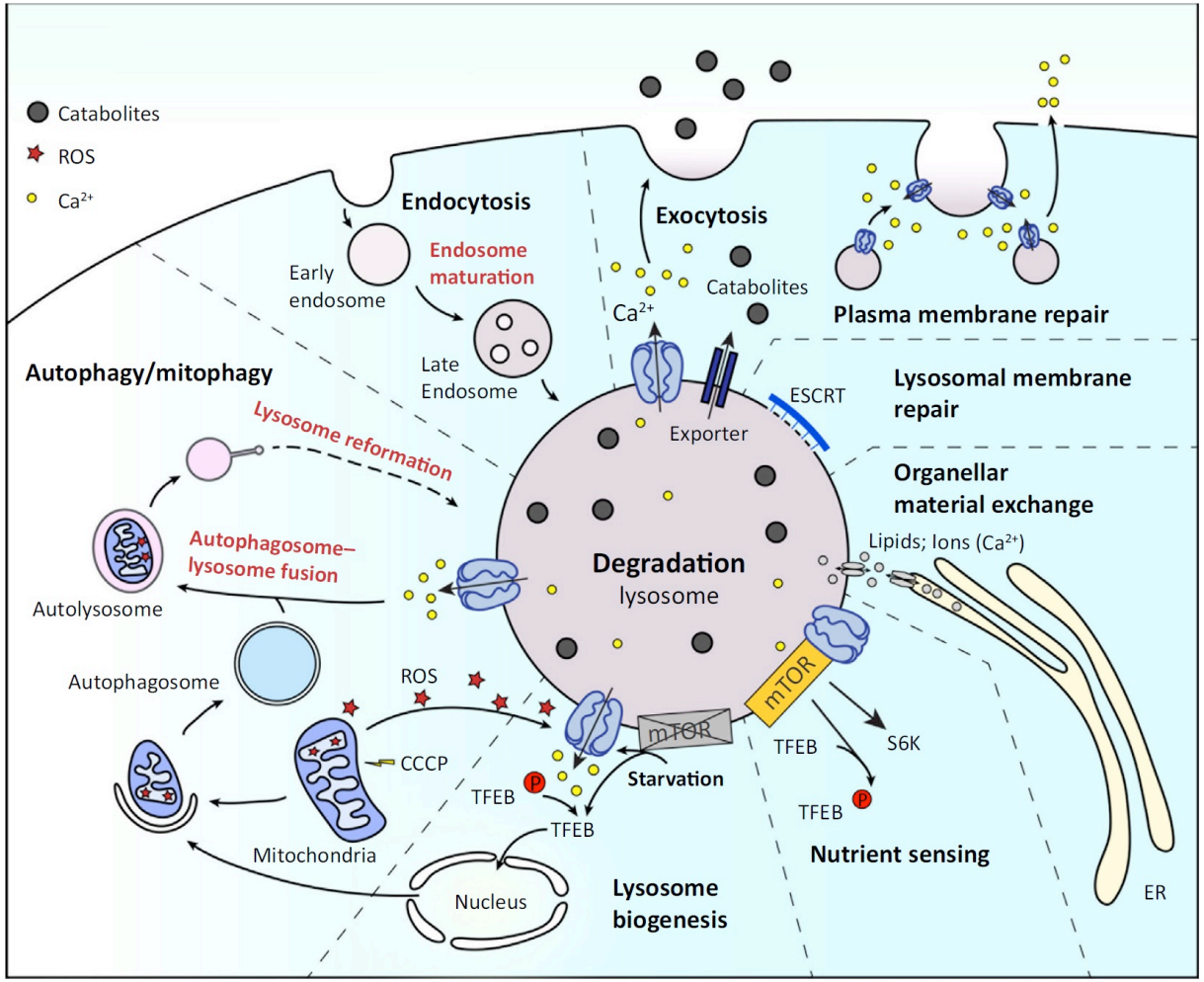
Case #4 - Echo

- Hypertrophic cardiomyopathy identified on cardiac echo
- Ejection fraction 20%

Ann & Robert H. Lurie
Children's Hospital of Chicago®

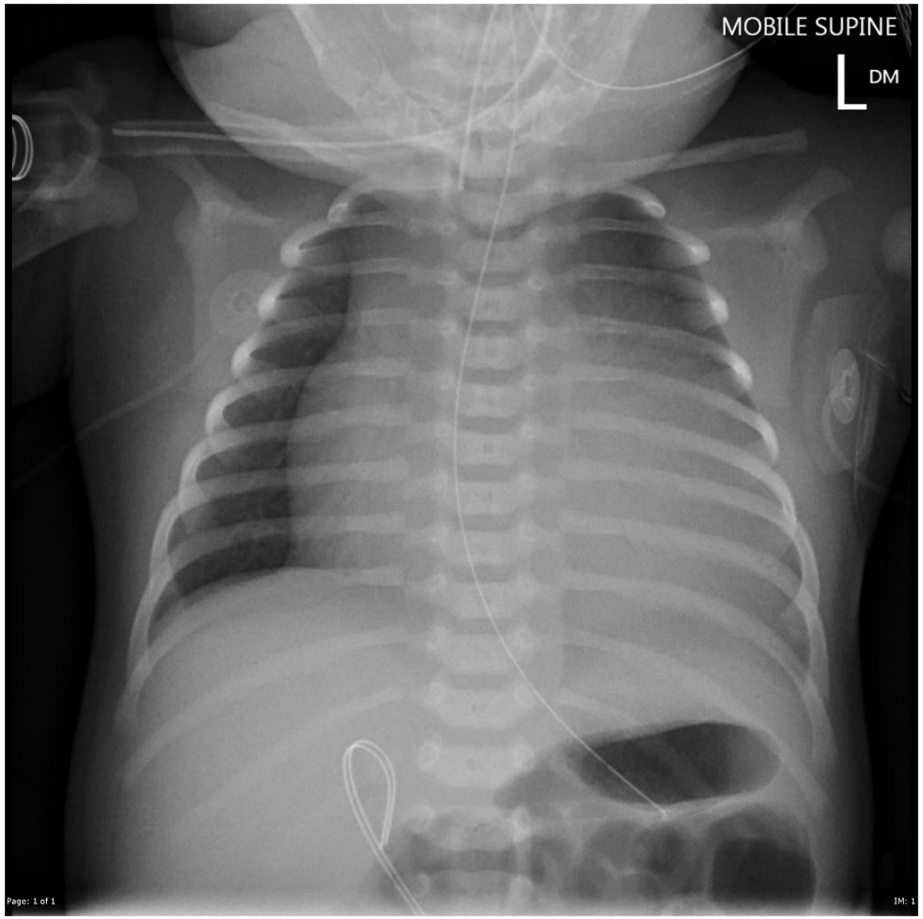
Lysosomal Storage Disorders

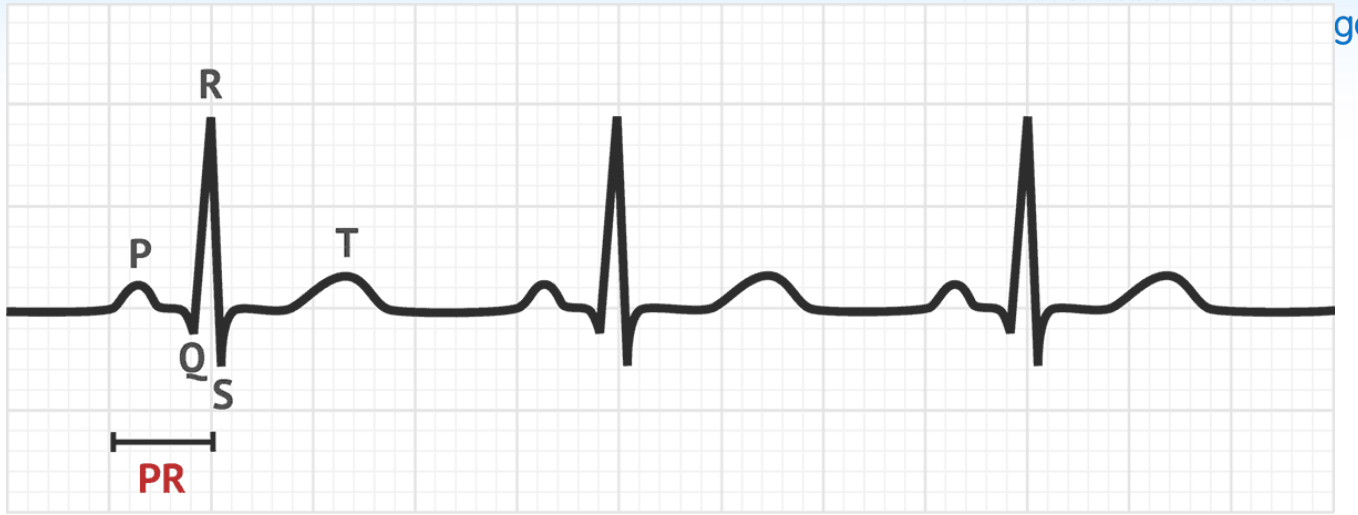
Lysosome: Function and Regulation



Ann & Robert H. Lurie
Children's Hospital of Chicago®

Pompe Disease


MOBILE SUPINE
L
DM


R
P
T
Q
S
PR


Hypotonia
(decreased
muscle tone)
A.D.A.M.

Resources

New England Consortium for Metabolic disorders

newenglandconsortium.org

Star-G Newborn screening

newbornscreening.info/Parents/facts.html

OMIM

Gene Reviews

ACMG ACT Sheets & Algorithms

Ann & Robert H. Lurie
Children's Hospital of Chicago®

Questions?

jobaker@luriechildrens.org

Ann & Robert H. Lurie
Children's Hospital of Chicago®

Case - Extra

Ann & Robert H. Lurie Children's Hospital of Chicago®

Case Presentation

- Newborn term breast-fed male
- Birth at 38 2/7; G3P1>2
- Uneventful prenatal care
- Feeding well; gaining wait
- NBS showed elevated ”C5-DC”

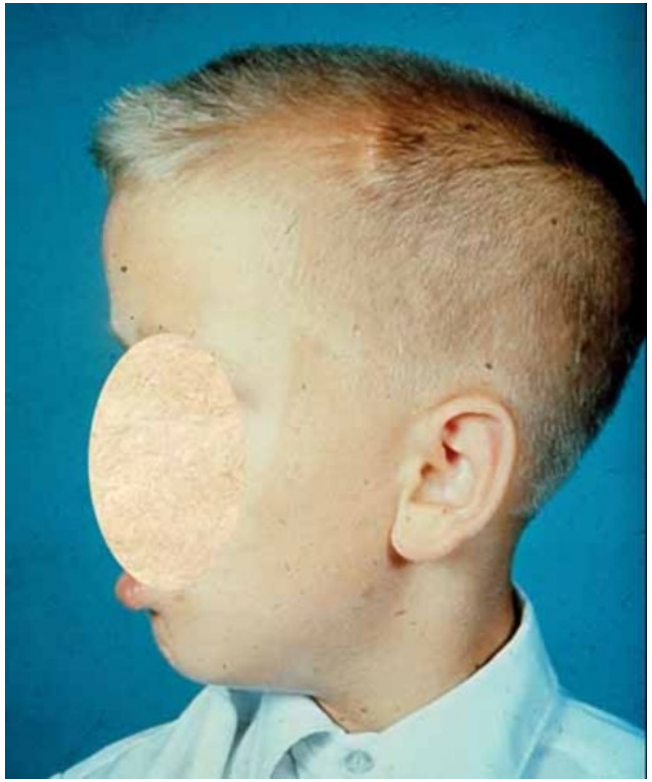
- Pediatrician calling
  - How urgent is this?
  - Baby doing well, but does he need to go to ER? Clinic? Referral and wait for a call?

Ann & Robert H. Lurie Children's Hospital of Chicago®

Diagnosis – Glutaric Acidemia

- NBS
  - C5-DC (96% sensitivity)
- Elevated concentration of 3-OH-GA in plasma or urine on biochemical testing
- Macrocephaly or MRI Findings
- Encephalopathic Crisis
- Whole Exome Sequencing

- Headaches, vertigo, dementia, and ataxia



American College of Medical Genetics **ACT SHEET**

Newborn Screening ACT Sheet
[Elevated C5-DC Acylcarnitine]
Glutaryl-CoA Dehydrogenase Deficiency

Differential Diagnosis: Glutaric aciduria (GA-1)

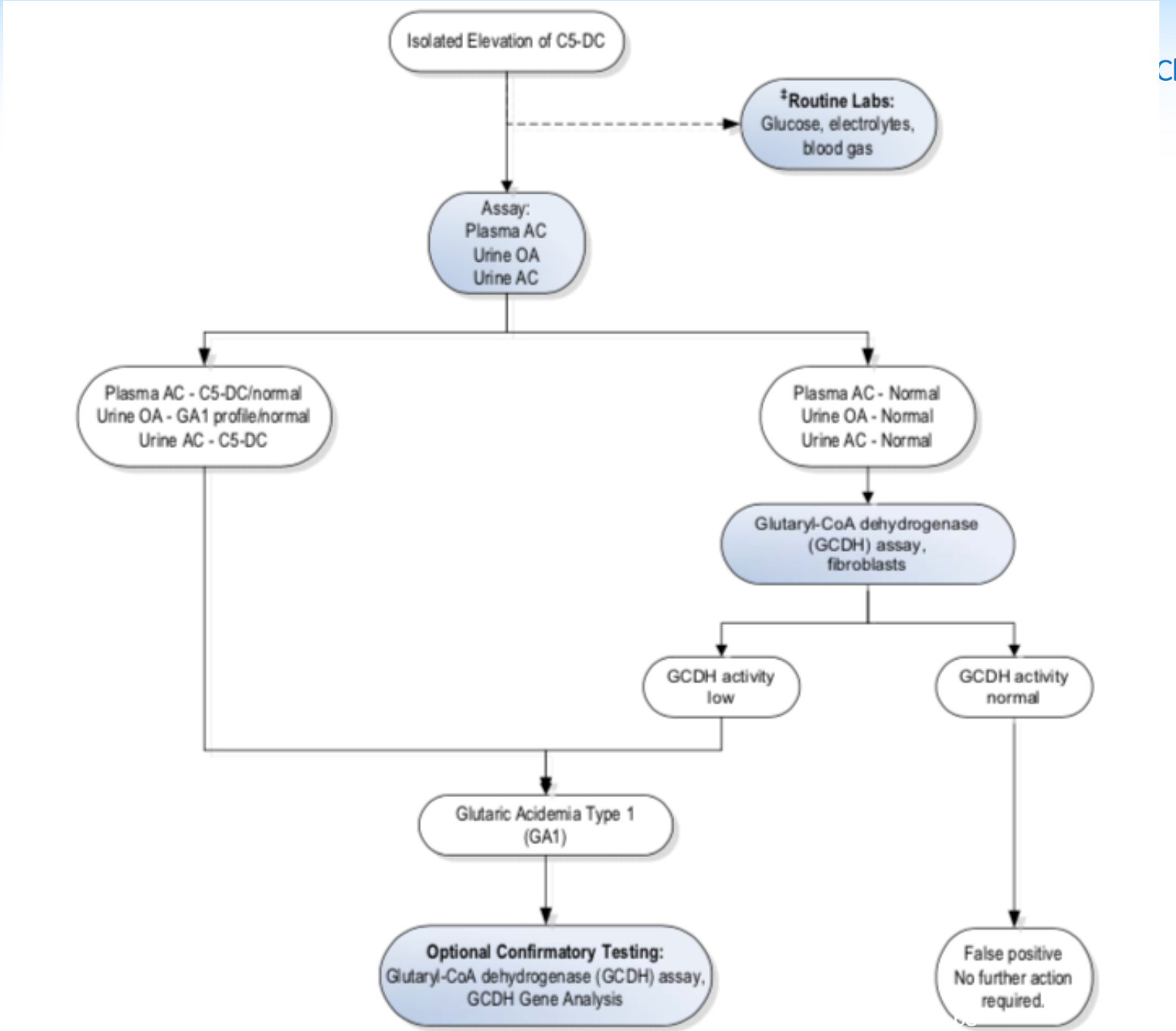
Condition Description: GA-1 is caused by a defect of **glutaryl-CoA dehydrogenase** which limits the metabolism of glutaryl-CoA to crotonyl-CoA, resulting in increased glutaric acid or its metabolites that are toxic.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

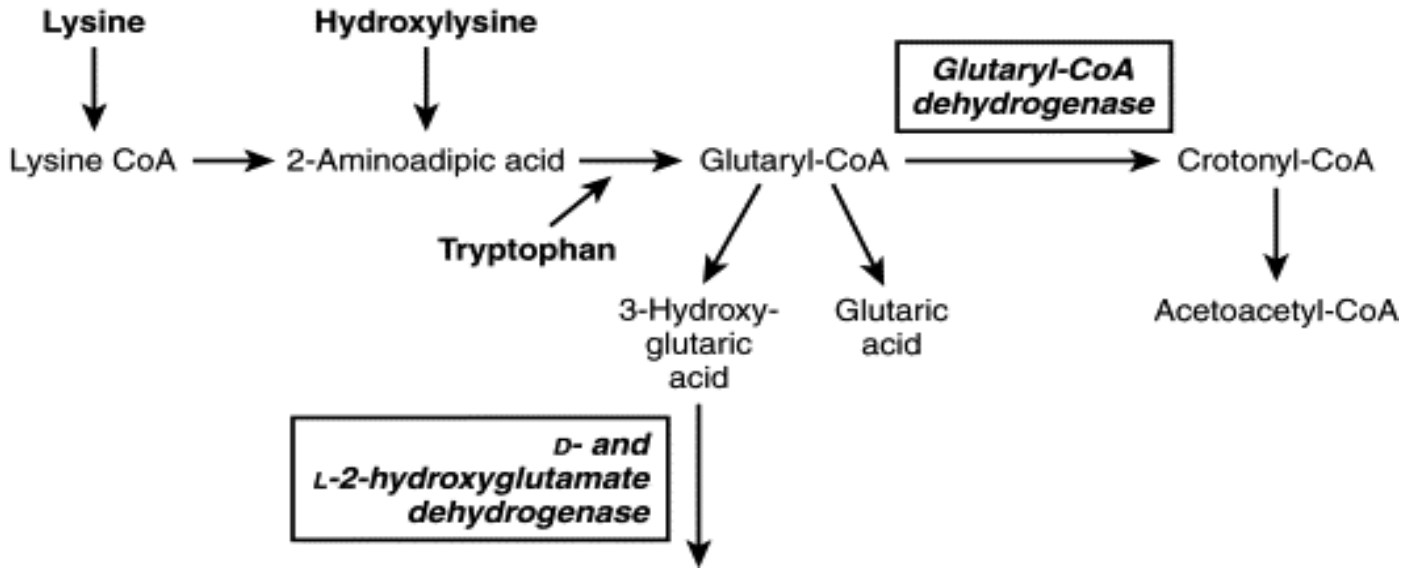
- Contact family **IMMEDIATELY** to inform them of the newborn screening result.
- Consult with pediatric metabolic specialist.
- Evaluate the newborn for macrocephaly and muscle hypotonia, initiate confirmatory/diagnostic testing as recommended by metabolic specialist.
- Refer to metabolic specialist to be seen as soon as possible but not later than three weeks.
- Educate family about diagnostic possibilities, complexity of diagnostic work-up and the possibility of neurodegenerative crisis with an intercurrent infectious illness.
- **IMMEDIATE** treatment with IV glucose is needed for intercurrent infectious illness.
- Report findings to newborn screening program.

Diagnostic Evaluation: Urine organic acid analysis should be ordered promptly, and will be diagnostic if it shows increased 3-hydroxyglutaric acid with or without increased glutaric acid. If urine organic acids don't confirm the diagnosis, the metabolic specialist will consider analyzing glutarylcarnitine in urine and 3-hydroxyglutaric acid in blood and CSF, enzyme assay in fibroblasts, and molecular analysis of the GCDH gene.

Clinical Considerations: The neonate with glutaric acidemia type I is usually macrocephalic but otherwise asymptomatic. Later signs include metabolic ketoacidosis, failure to thrive, and sudden onset of dystonia and athetosis due to irreversible striatal damage. With appropriate treatment, 60-70% of patients will not suffer neurodegenerative disease.

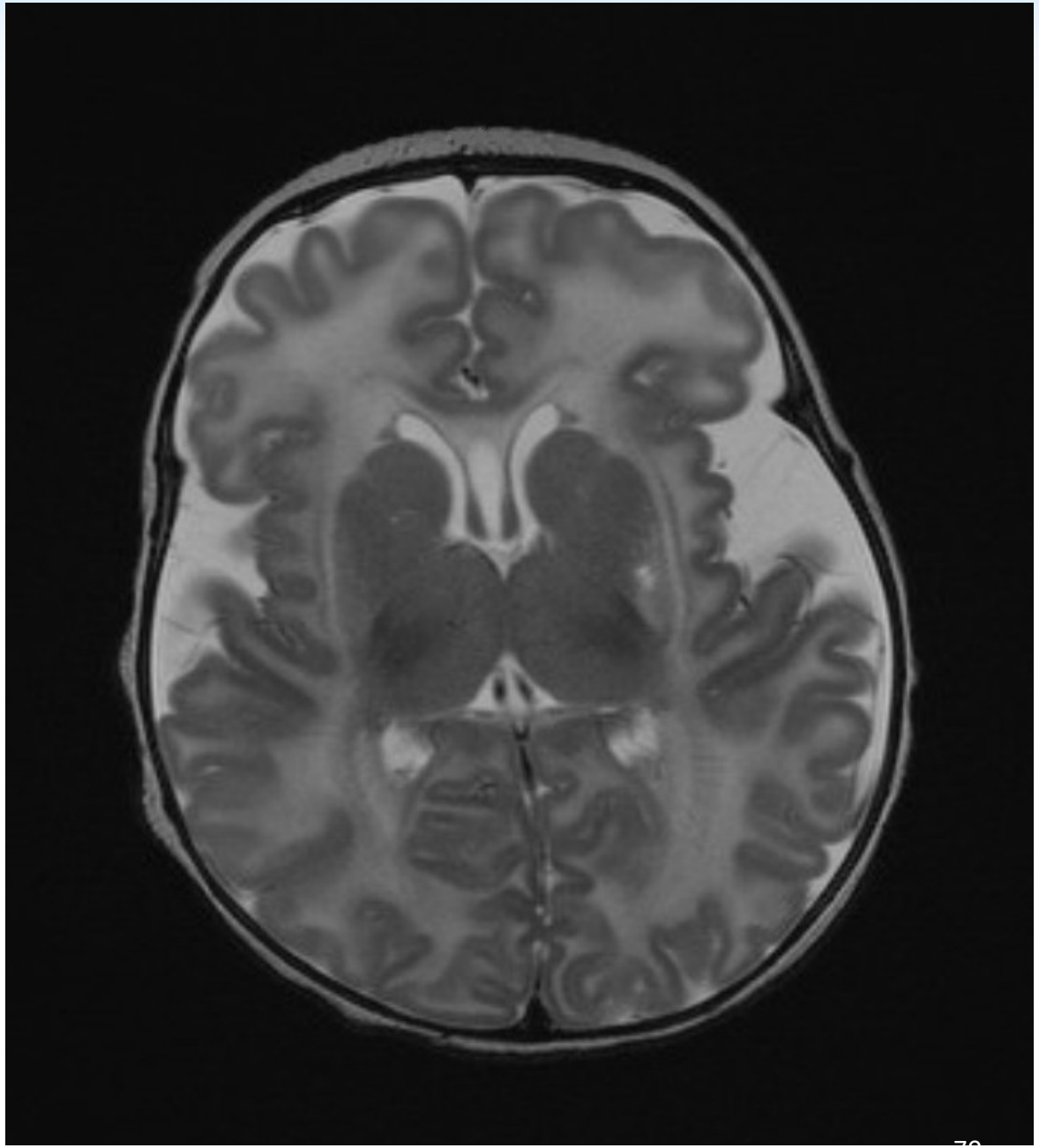

Isolated Elevation of C5-DC
‡Routine Labs:
Glucose, electrolytes,
blood gas
Assay:
Plasma AC
Urine OA
Urine AC
Plasma AC - C5-DC/normal
Urine OA - GA1 profile/normal
Urine AC - C5-DC
Plasma AC - Normal
Urine OA - Normal
Urine AC - Normal
Glutaryl-CoA dehydrogenase
(GCDH) assay,
fibroblasts
GCDH activity
low
GCDH activity
normal
Glutaric Acidemia Type 1
(GA1)
Optional Confirmatory Testing:
Glutaryl-CoA dehydrogenase (GCDH) assay,
GCDH Gene Analysis
False positive
No further action
required.

Biochemical Testing



- Glutaric Acid
- 3-hydroxyglutaric Acid
- Glutaryl carnitine
- Glutaconic Acid

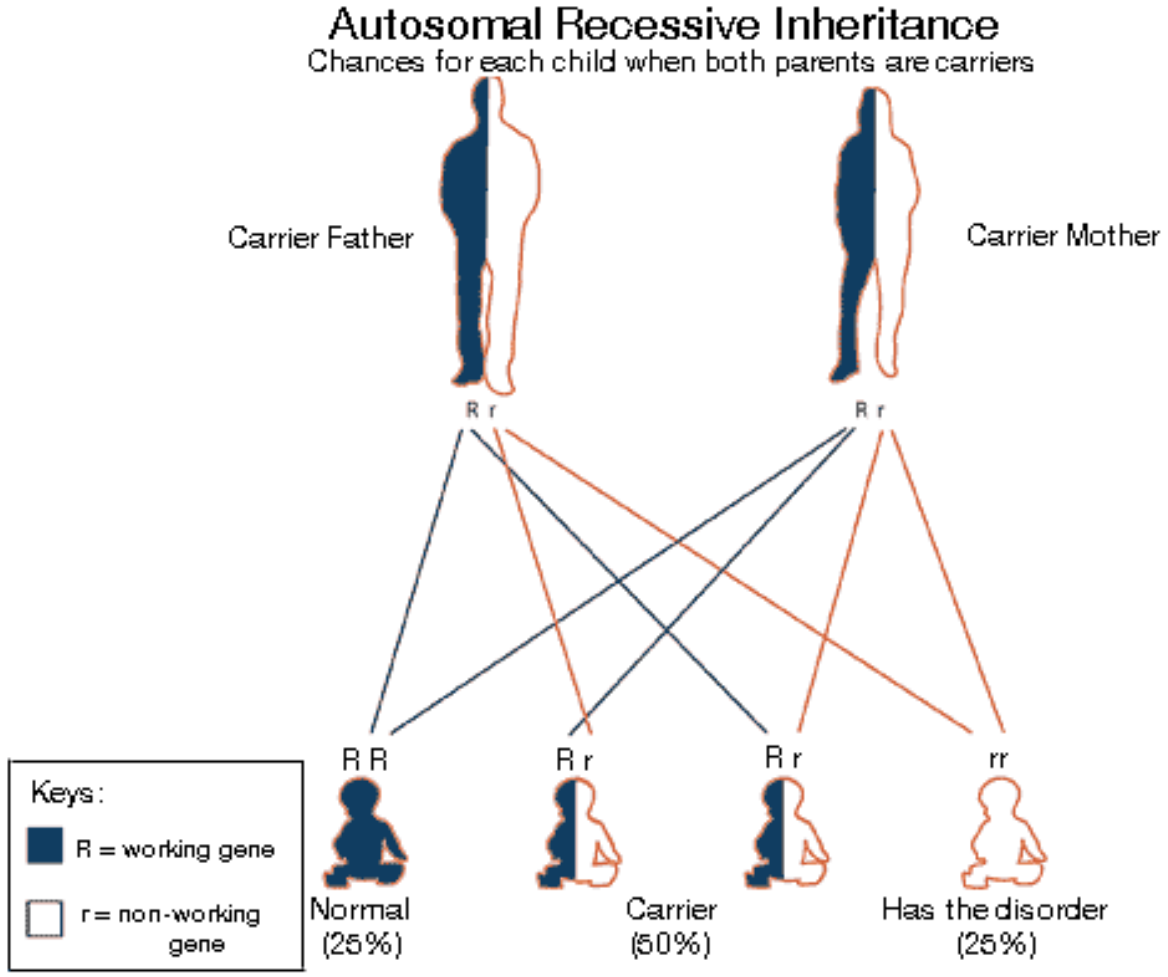
MRI Findings



Molecular Testing

- *GCDH*
  - Sequencing + Del/Dup
  - c.553_570del18
- Fibroblast Studies
- Testing of at risk sibs

- Genetic Counseling

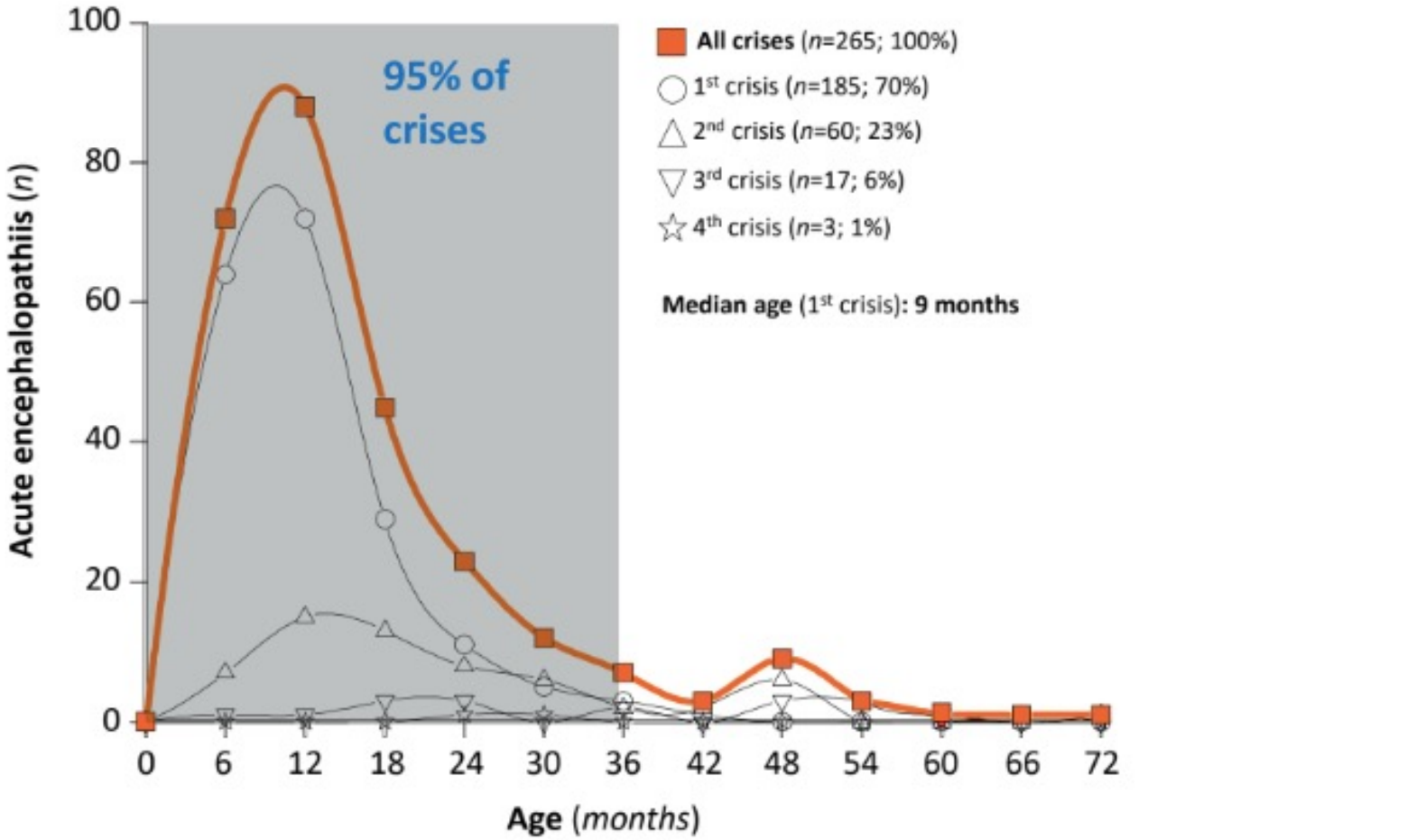


Natural History

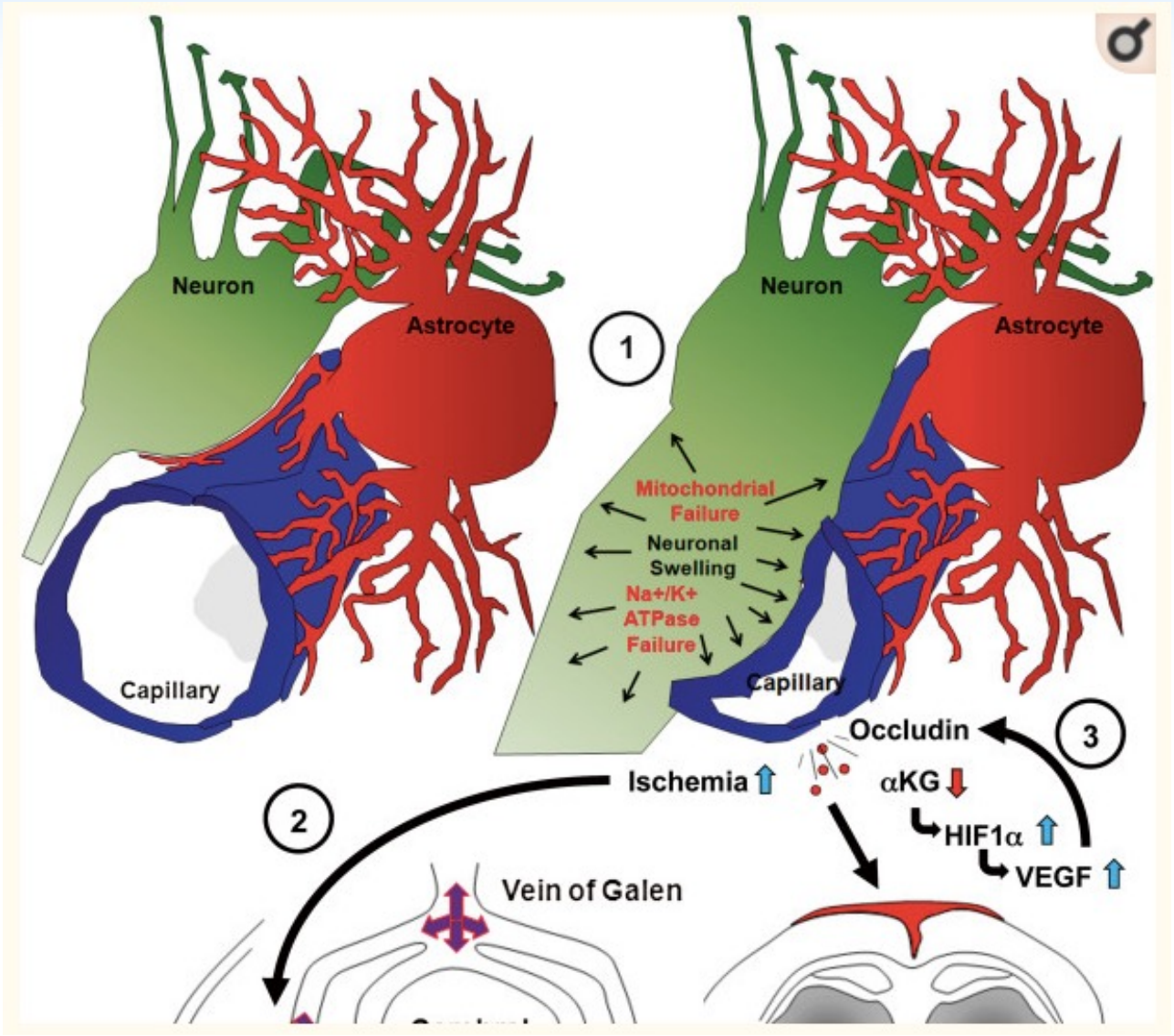
- Encephalopathic Crisis
  - Untreated - 80-90%
  - Treated – unclear
- Subdural Hemorrhages
- Seizures ~7%
- Kidney Disease

Acute encephalopathic crises

'Window of vulnerability'



Kölker et al. *Pediatr Res*; 59: 840-847 (2006)



Zinnanti WJ, Lazovic J, Housman C, et al. Mechanism of metabolic stroke and spontaneous cerebral hemorrhage in glutaric aciduria type I. *Acta Neuropathol Commun*. 2014;2:13. Published 2014 Jan 27. doi:10.1186/2051-5960-2-13

Treatment – Acute Care

At Risk Times…

- Fever
- Surgery
- Delivery/Pregnancy
- Prolonged Fasting
- Excessive dietary protein intake
- Inadequate chronic caloric intake

Management

- Lysine free protein vs stopping protein intake
- Adequate alternative calories
  - Dextrose +/- IL
- Carnitine Dosing
- Antipyretics
- Stopping offending stress

Ann & Robert H. Lurie Children's Hospital of Chicago®

Baseline Dietary Guidelines

Table 5.

Nutritional Requirements for L-lysine, L-Carnitine, Calories, and Natural Protein for Infants and Children with GA-1

	0-6 mos	7-12 mos	12-47 mos	48-72 mos	>6 yrs
L-lysine (from dietary natural protein), [1] mg/kg/day	100	90	60-80	50-60	Controlled protein intake w/natural protein & low-Lys content, avoiding Lys-rich foods
Protein from GA-1-specific Lys-free, Trp-restricted formula, [2] g/kg/day	0.8-1.3	0.8-1.0	0.8	0.8	Generally no requirement for GA-1-specific amino acid formula
Energy, kcal/kg/day	80-100	80	81-94	63-86	As per normal pediatric requirements, guided by age & weight
L-carnitine, mg/kg/day	100	100	100	50-100	30-50

Manifestation/Concern	Evaluation	Frequency/Comment
Poor growth	Measurement of growth, weight, & head circumference	At each visit
Delayed acquisition of developmental milestones	Monitor developmental milestones.	At each visit
	Neuropsychological testing using age-appropriate standardized assessment batteries	As needed
	Standardized quality-of-life assessment tools for affected individuals & parents/caregivers	As needed
Movement disorder	Assessment for clinical symptoms & signs of movement disorders, severity, & responses to treatment, physical therapy, & pharmacologic interventions	At each visit
Abnormal amino acid levels (amino acid deficiencies & ↑ lysine)	Quantitative analysis of plasma amino acids (ideally obtained after a 3-hr protein fast) [1]	• 1st year of life: at least every 3 mos • Ages 1-6 yrs: every 6 mos • >6 yrs of age: annually
Nutritional deficiencies [2]	Calcium, phosphorus, vitamin D, prealbumin, B_{12}, zinc, ferritin	If clinically indicated [3]
Chronic renal insufficiency [4]	Plasma creatinine &/or cystatin C level	Periodically in adolescents & adults
Anemia	Complete blood count, ferritin level	If clinically indicated [3]
Abnormal liver function	ALT/AST , albumin	If clinically indicated [3]
Head injury [5] &/or rapid head growth [6]	Consider head MRI.	If clinically indicated [7]