Metabolic Disorders

Walaa Alshuaibi, MD
Assistant Professor of Pediatrics
Medical Genetics Consultant
Department of Pediatrics
King Saud University, College of Medicine
King Khalid University Hospital

Question

A two-week-old female infant presents with a several day history of lethargy and poor feeding, with repeated vomiting. The infant was a product of a normal pregnancy and an uneventful vaginal delivery.

Birth weight was 3810 gm; today's weight is 3520 gm. The infant is jaundiced, and has a weak, high-pitched cry. The liver edge is palpable 2 cm below the right costal margin.

Complete blood count is unremarkable. Total indirect (unconjugated) bilirubin is elevated. Urine is positive for reducing substances when tested by the clinitest method, although a standard urinalysis is unremarkable. Blood glucose is 42 mg/dl. Which of the following is the most likely diagnosis?

1. Sepsis
2. Subdural hematoma
3. Formula intolerance
4. Neonatal hepatitis
5. Galactosemia

a 7-day-old male infant; he was born at term. He is the 3.5 kg product of an uncomplicated pregnancy, labor and unassisted vaginal delivery of a 27-year-old g_2p_1ab0 woman; the patient presents with the sudden onset of vomiting, lethargy, and tachypnea. He is bottle-fed and was feeding vigorously until today. He has had no fever, rhinorrhea, cough, diarrhea, or abdominal distention. An older sister had the onset of similar symptoms at 5 ½ years of age, as did their mother, in both of whom these symptoms would recur episodically, usually with an intercurrent infection. A maternal uncle died in infancy with very similar symptoms; he also experienced seizures. Examination reveals a normal temperature, a pulse of 134, a blood pressure of 88/52 mm hg, and a respiratory rate of 62. He is lethargic. The anterior fontanelle is slightly sunken. There is mild skin tenting and moderate hypertonia. The lungs are clear. There is no organomegaly or petechiae. You obtain blood, urine, and cerebrospinal fluid cultures, all of which are pending. Cerebrospinal fluid cell count, glucose, and protein are normal. Chest radiography is normal. An arterial ammonia level is 1,650 mcg/dl. Ketones are normal.

what type of disorder best accounts for this patient's clinical picture?

1. UCD Urea cycle defect
2. Aminoacidopathy
3. OA
4. FAO
5. Lysosomal storage

Case

You are asked to evaluate a 4-day-old male infant; he was born at term. He is the 3.1 kg product of an uncomplicated pregnancy, labor, and unassisted vaginal delivery of a 24-year-old $g_1p_0ab_0$ woman. There was a positive newborn screening test for phenylketonuria (PKU). The child's mother reports that he appears to be completely well; he has been breast feeding without difficulty or vomiting. Physical examination is entirely normal.

Question

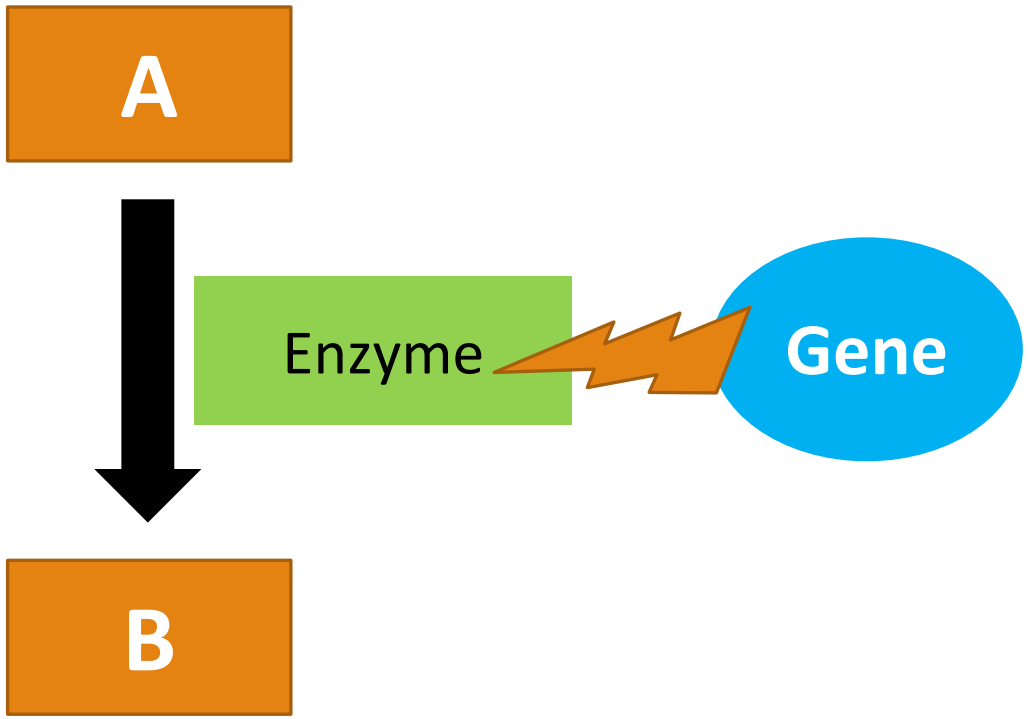
what would you tell this child's mother?

1. Most positive results are FP, need to repeat screen in 2 weeks
2. Since child is feeding well, no need for further evaluation
3. He child need to start immediately on phe- restricted diet
4. Most positive results are true positive, so most likely your son has PKU
5. He child needs plasma phe and tyrosine level

Introduction

- Each of us is made of large complex molecules.
- They form tissues and organs.
- Molecules are NOT static
- Catalytic steps mediated by enzymes, encoded by genes
- Mutations in those genes, will lead to enzyme deficiency , leading to “inborn Error of Metabolism”

Or metabolic disorders



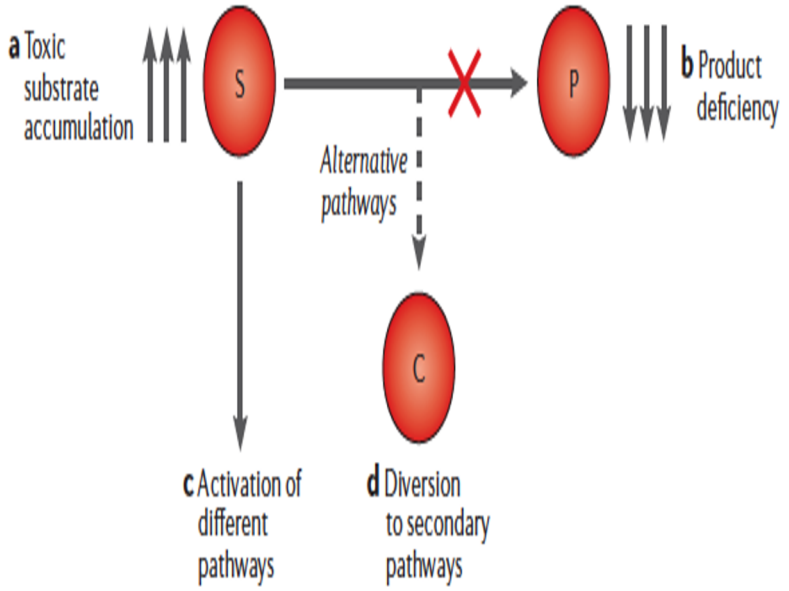
Inborn Error of Metabolism (IEM)

- Group of congenital disorders caused by an inherited defect in a single specific enzyme that results in a disruption in a specific metabolic pathway.

- Individually rare, but collectively common.

  Eg. if there are 50 IEM each one of them are rare , لكن لما ناخذ الخمسين على بعض actually not rare

- Mechanism of actions:
  - Direct toxicity of the accumulating substrate
  - Deficiency of the product
  - Activation of alternative pathways or diversion to secondary pathways leading to toxic byproducts



Lanpher et. al., nature 2006

Cont. IEM

- Consider in neonate with presumed sepsis or acidosis; older child with acidosis, lethargy
- Usually term infant, good Apgars bc fetus using mother enzyme, once they born the problem start showing.
- Family Hx usually negative – may see consanguinity. -ve FHx doesn't rule out, +ve increase suspicion.We consider a couple of the same tribe as consanguinity.
- Sx – generally non specific with poor feeding, irritability, vomiting, seizures, progressing to lethargy, coma, apnea
- Occasionally specific sx/clues – urine odors, skin/hair
- All autosomal recessive except OTC and Hunter disease those are X-linkeddisease

Differential Diagnosis of newborn with vomiting, lethargy, sz …

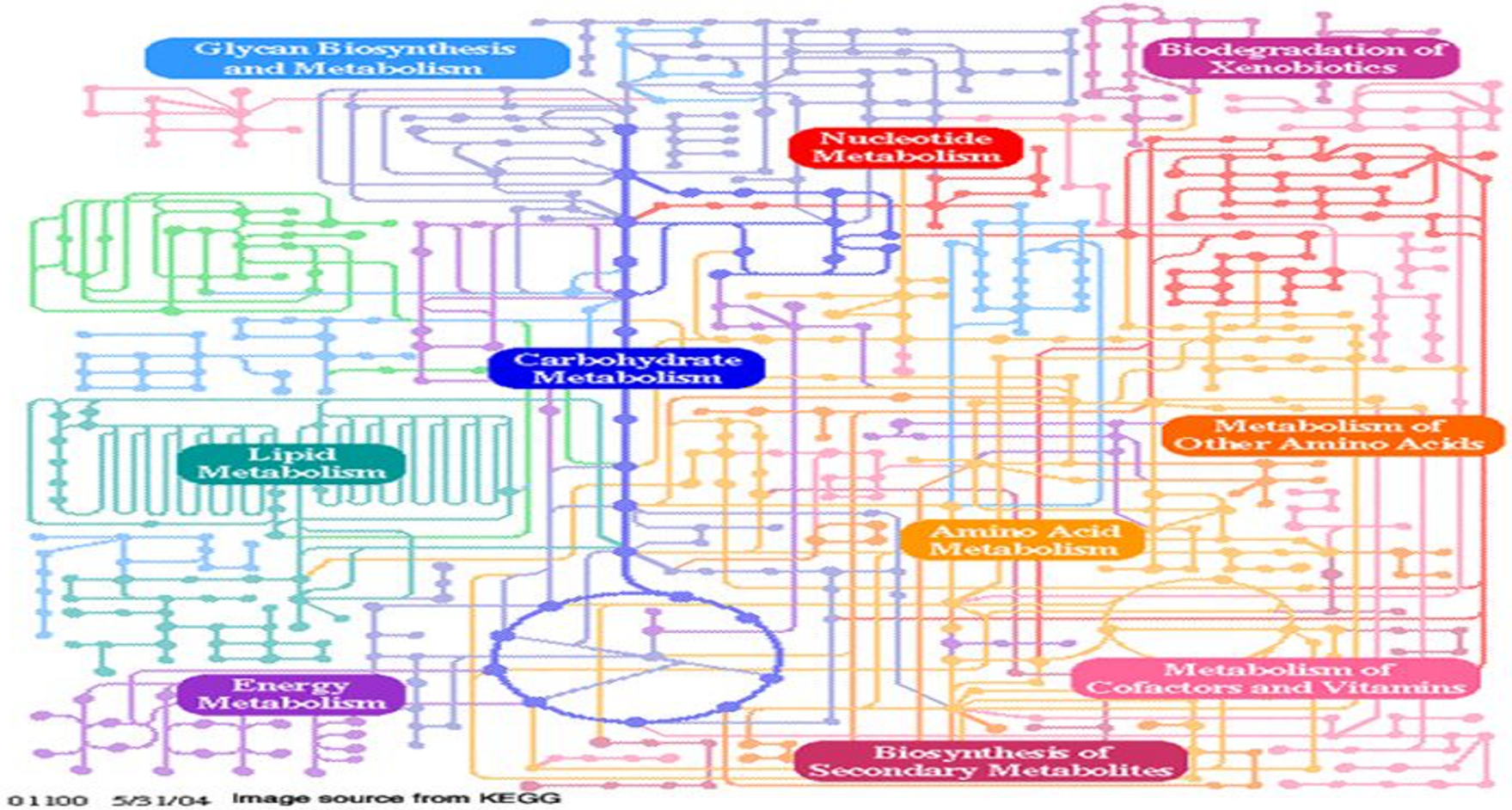
- Amino acid disorders: MSUD
- Urea cycle disorders
- Organic acid disorders
- Carbohydrate disorders : congenital lactic acidosis, fructose disorders
- Mitochondrial disorders
- FAO disorders
- Other: **(** sepsis, adrenal insufficiency, CHD, asphyxia **)** think about them first bc common is common then think about metabolic disorder
- Sepsis more common than MD especially in neonate

Fat

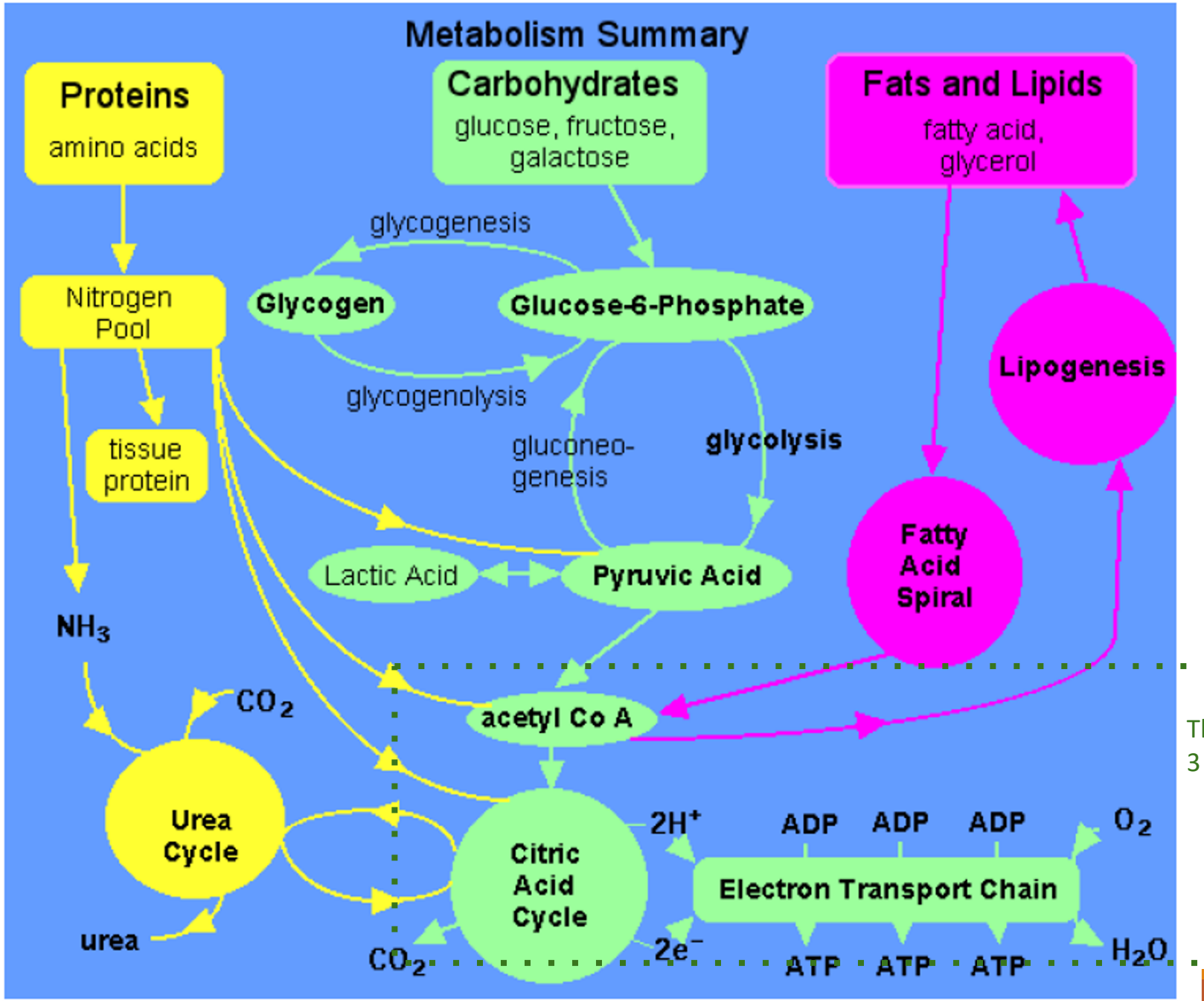
Carbohydrate

Protein

Complexity of inborn errors of metabolism



just to refresh مو لازم تحفظوه



The end result of all those 3 pathways

Disorders of Amino Acids

مو لازم تحفظوها

Essential & Non-Essential Amino Acids

Essential Amino Acids:

The body can't produce it, we get it from the food.

- Arginine
- Isoleucine
- Histidine
- Leucine
- Methionine
- Lysine
- Phenylalanine
- Tryptophan
- Threonine
- Valine

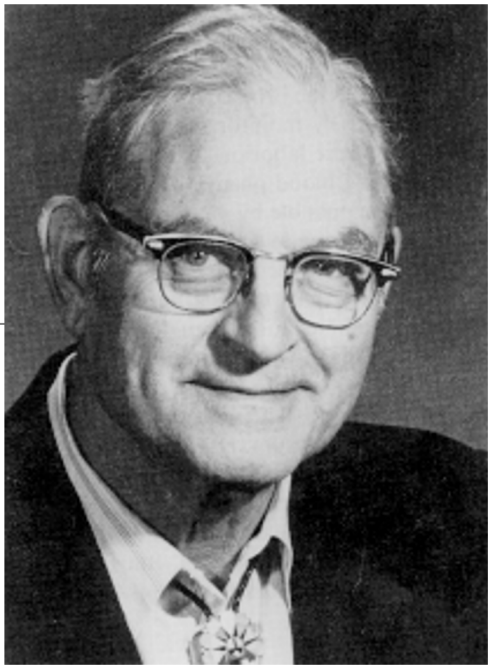
Non-Essential Amino Acids:

The body can produce it

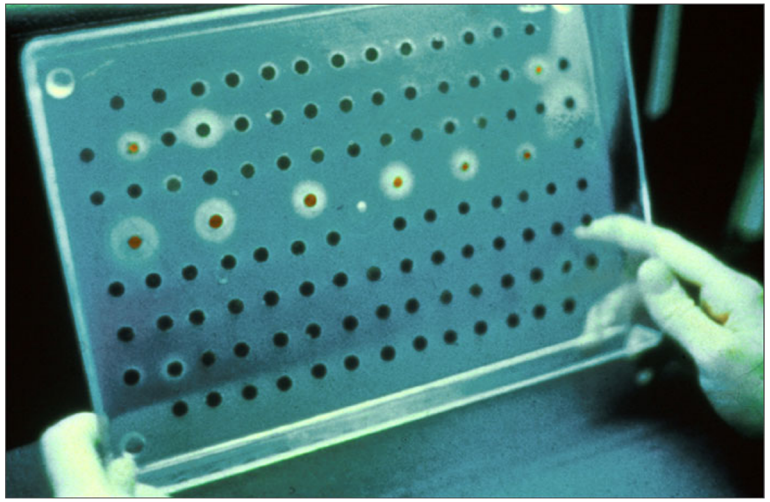
- Alanine
- Arginine
- Asparagine
- Aspartic Acid
- Cysteine
- Glutamic Acid
- Glutamine
- Glycine
- Proline
- Serine
- Tyrosine

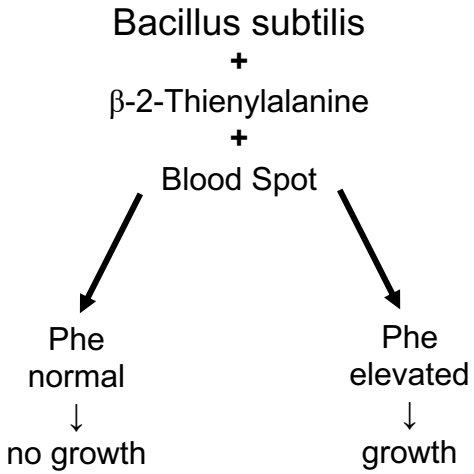
Phenylketonuria

Is the first Metabolic disorder has been discovered



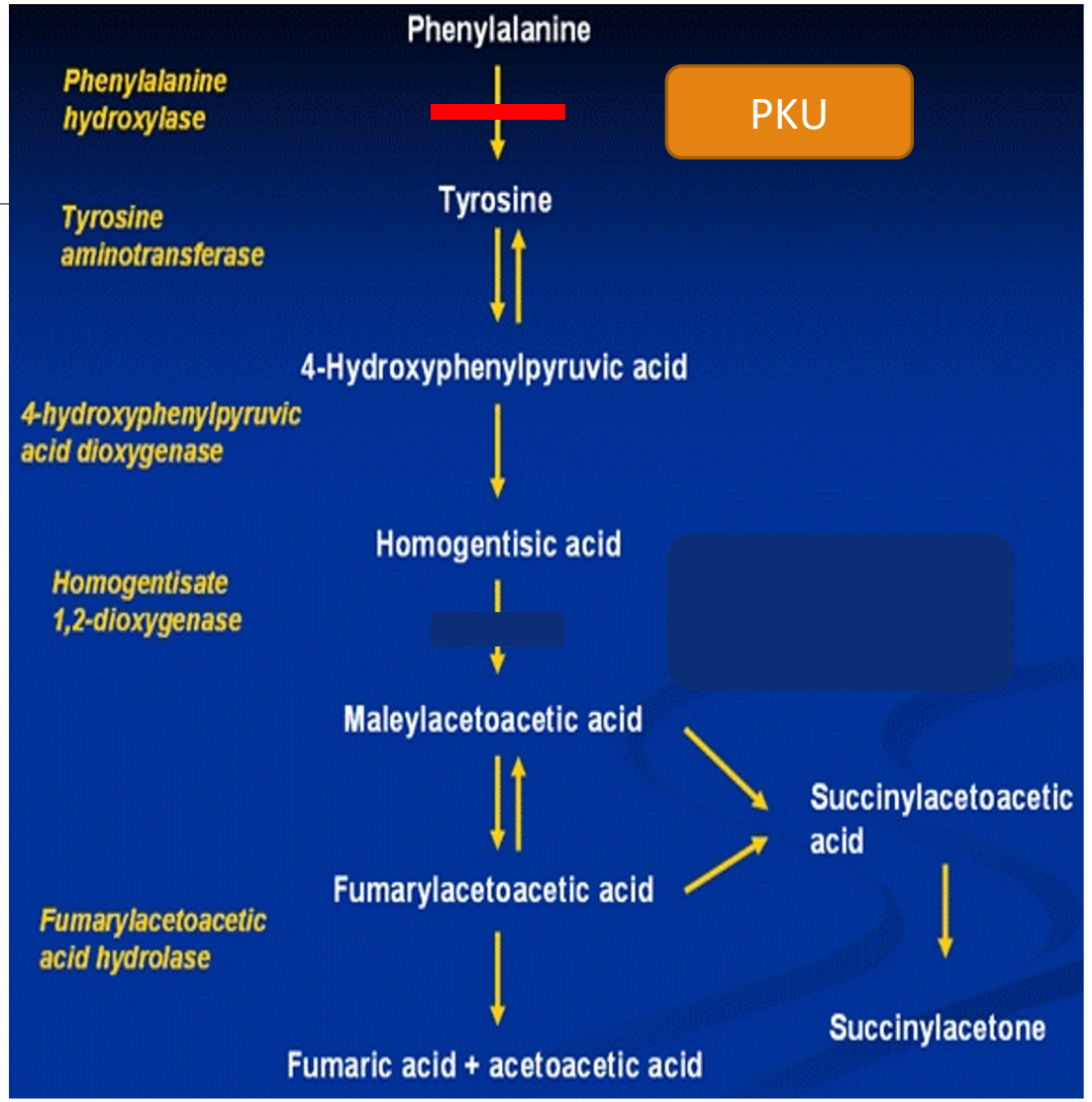
- Robert Guthrie: 1916–1995
- Adapted the bacterial inhibition assay to newborn screening for PKU
- Leading advocate for NB screening





Phenylketonuria

- Deficiency in phenylalanine hydroxylase
- Mousy odor
- light hair/ skin bc tyrosine involved in Melanin production, so if the pathway blocked the tyrosine will be deficient and phenylalanine will accumulate.
- Seizures
- Developmental delay, Autism, intellectual disability
- White matter hyperintensities
- Diagnosis: high phenylalanine, low tyrosine



PKU treatment

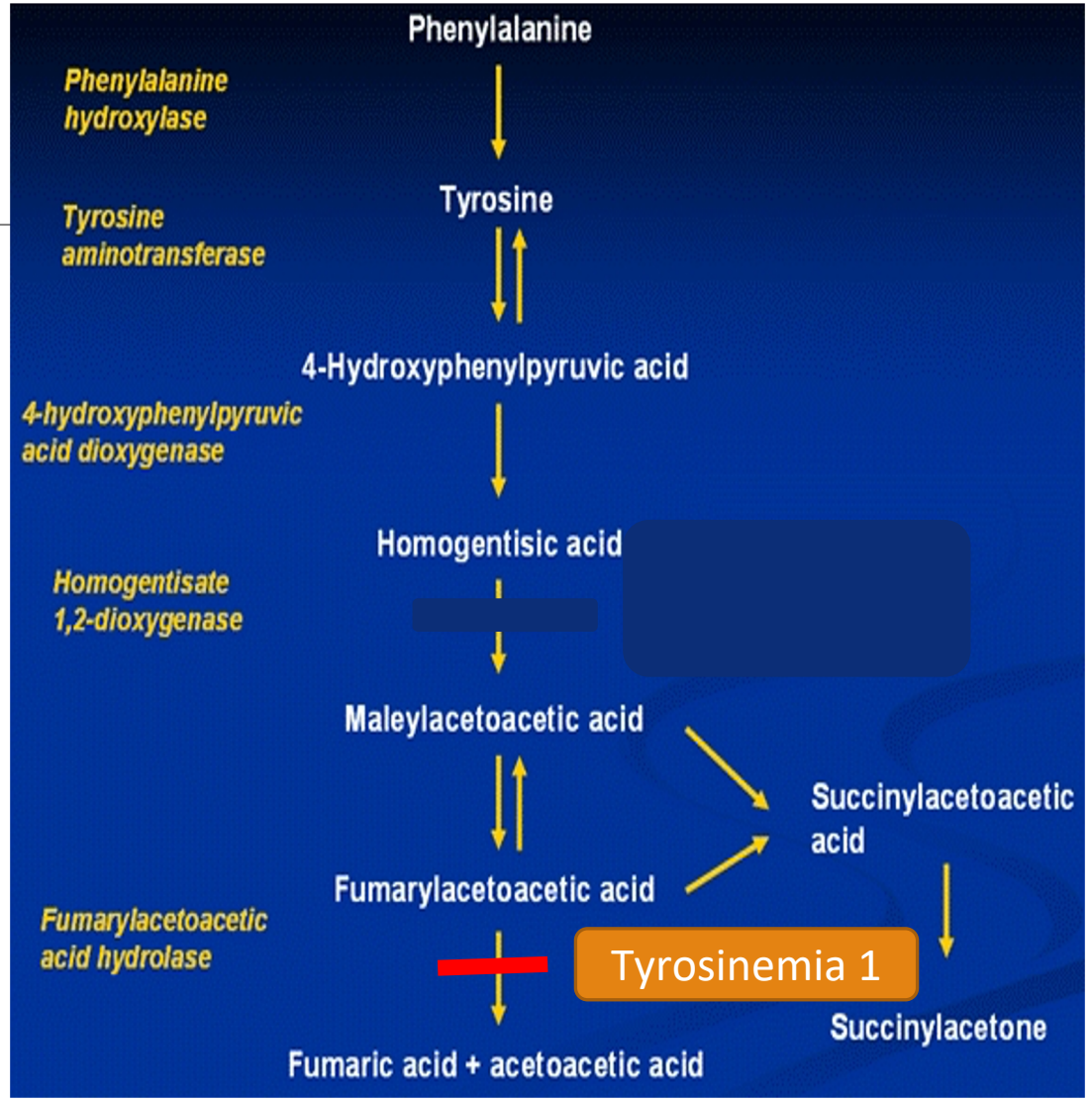
- “Diet for life”
- Restrict phenylalanine by restricting dietary protein
- Supplement with phenylalanine-free medical food to guarantee the daily requirements
- Supplement tyrosine and other needed AA

Maternal PKU

- A teratogenic issue
- Symptoms:
  - Microcephaly
  - Cognitive disability
  - Heart defects
- Management:
  - Planned pregnancies
  - Strict adherence to a low-phenylalanine diet
  - Management begins prior to conception

Tyrosinemia type 1

- Fumarylacetoacetate hydrolase deficiency for all disease here, , you don't have to remember enzymes name.
- Can presents with liver or renal disease
- Treatment:
  - NTBC
  - Phenylalanine and tyrosine restriction
  - Liver transplant if hepatocellular carcinoma develops



Homocystinuria

- Deficiency in the cystathionine B-synthase (CBS)
- Marfanoid habitus (?v.s. Marian) you have to now the differences between them is an exam question.
- patients will look like marfan tall, thin and long extremities compare with the trunk .
- Eye abnormalities
  - Ectopia lentis- lens displaced downward while in marfan upward
  - Myopia
- Developmental disability
- Neuropsychiatric symptoms
- Thromboembolism

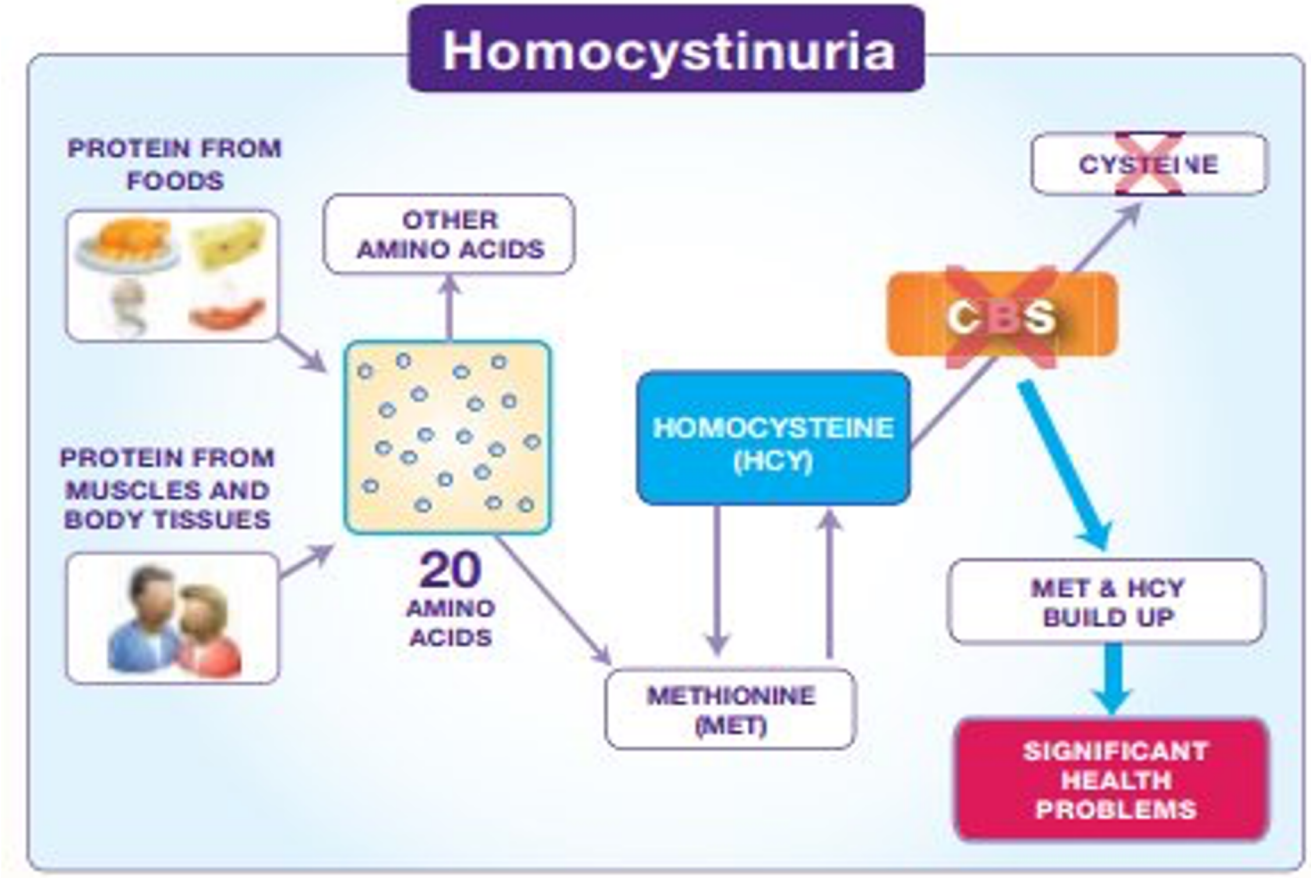
Extra pic.

Table 2 Difference between Homocystinuria and Marfan syndrome

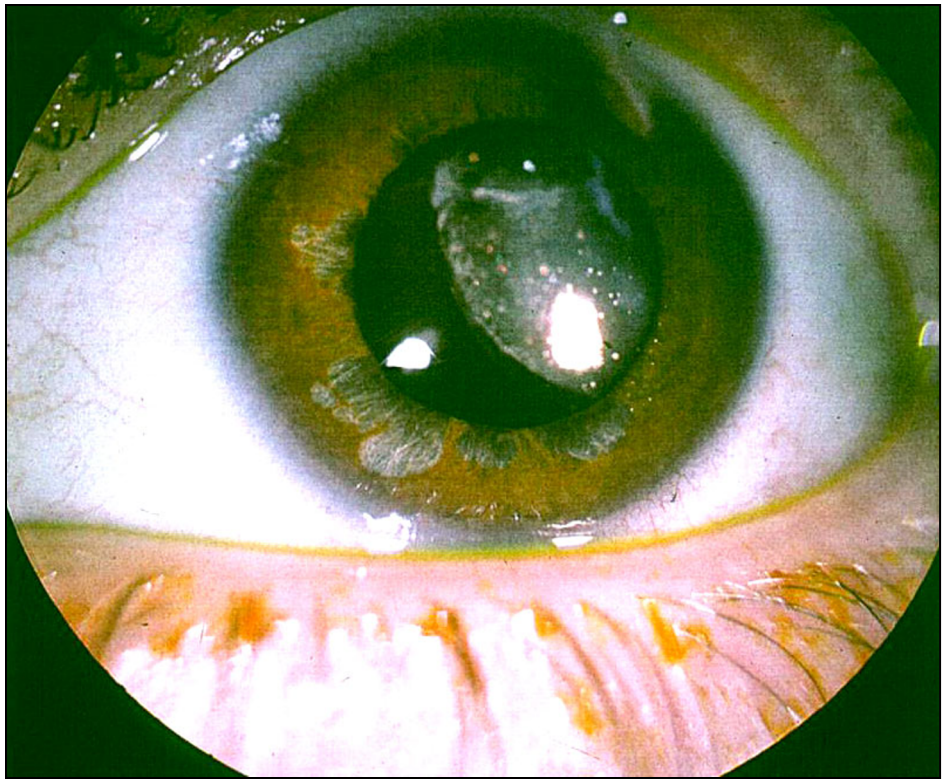
Homocystinuria	Marfan syndrome
Autosomal recessive	Autosomal dominant
Intellectual disability	Normal intelligence
Ocular lens usually dislocated downward (ectopia lentis)	Ocular lens usually dislocated upward (ectopia lentis)
Limited joint mobility	Lax joint (hyperflexibility)
Normal aorta	Aortic dilatation
Associated with thromboembolism	Not associated with thromboembolism

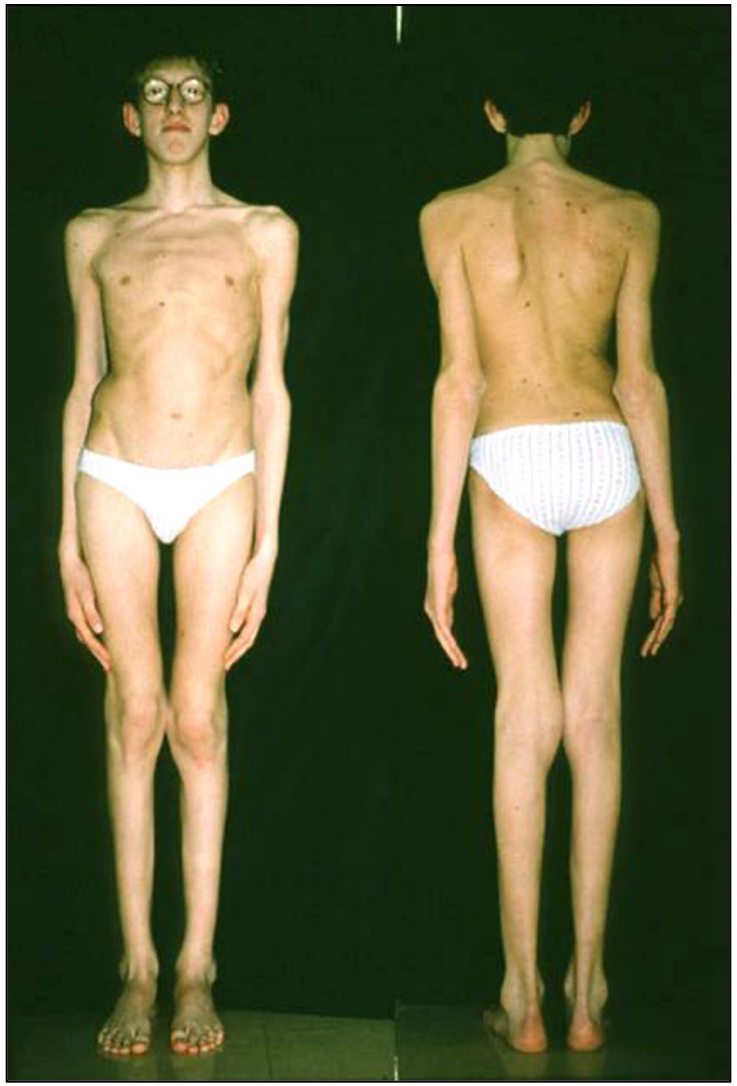
Homocytinuria (downward dislocation= low IQ),

Marfan syndrome, upward (upward= normal IQ)



Courtesy JM Saudubray





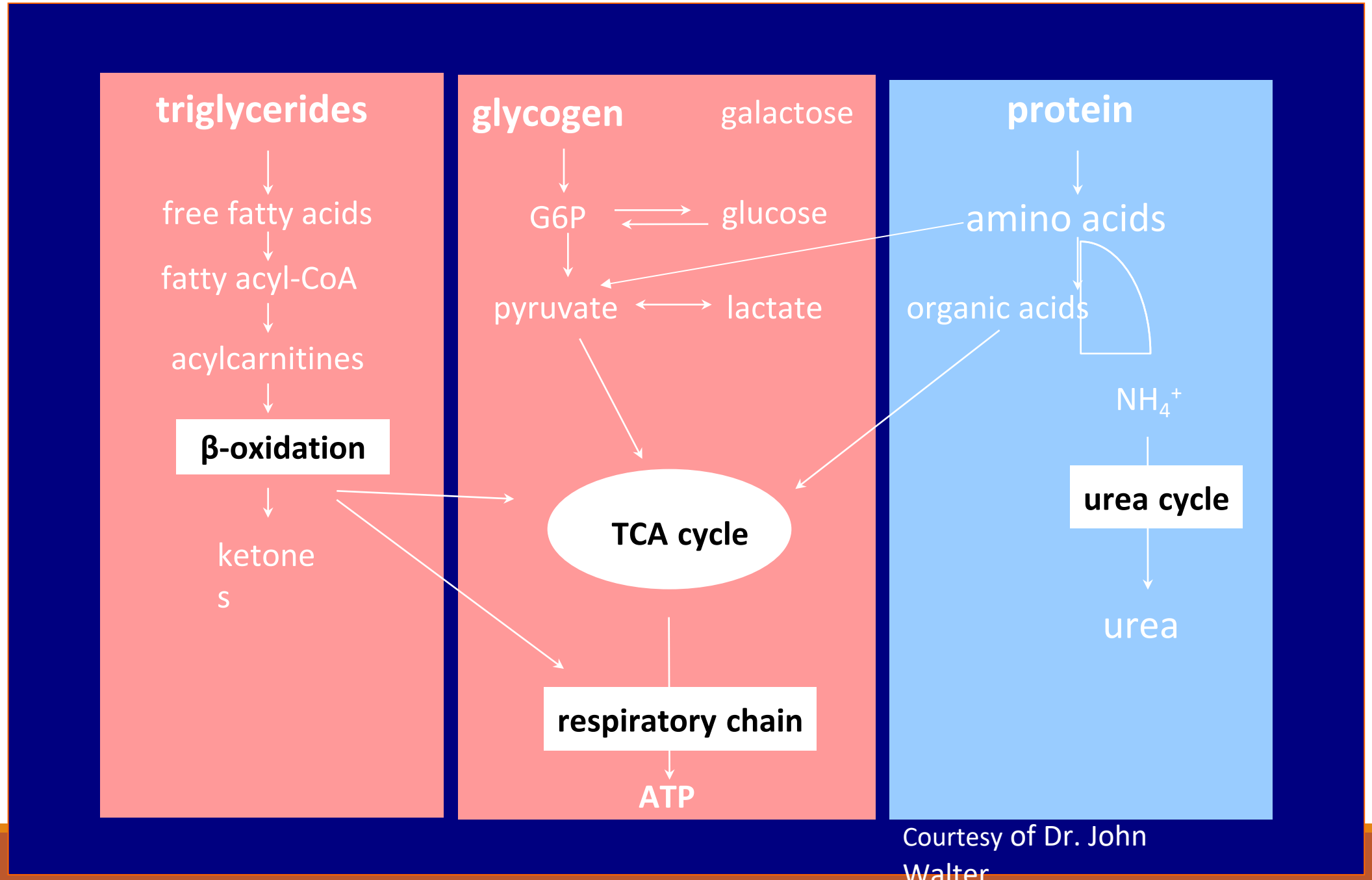
Homocystinuria Treatment

- Restrict dietary protein of Methionine and homocysteine,
- Always remember in metabolic disorder treatment is restoration not complete stoppage

Glutaric Aciduria Type I

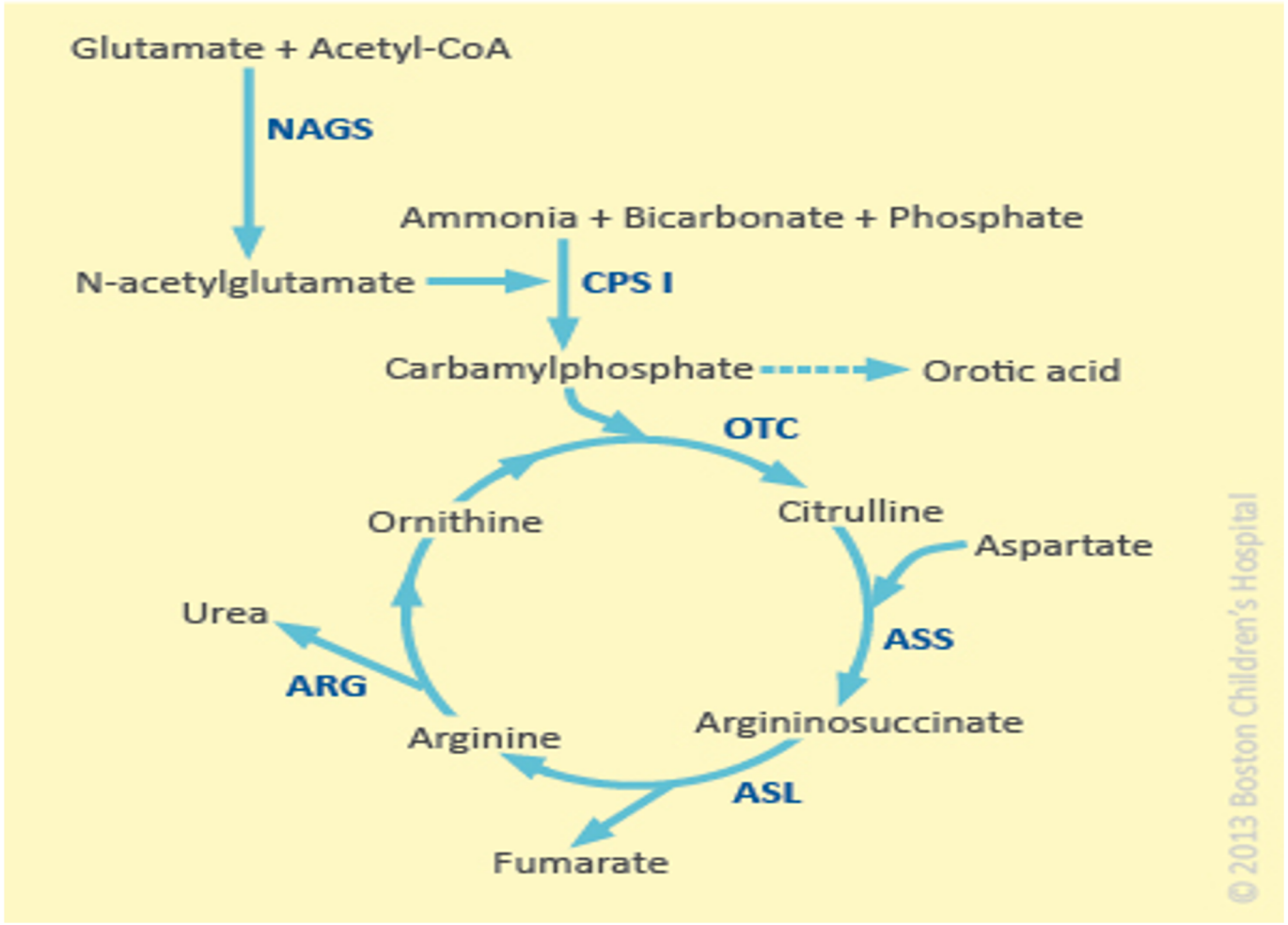
- macrocephaly; fronto-temporal atrophy
- acute encephalopathic crises
- IDD (intellectual and developmental disabilities), dystonia; MRI with basal ganglia changes and cortical atrophy
- Defect in lys/Trp metabolism (glutaryl CoA dehydrogenase)
- Dx urine organics with elevated glutaric, 3 OH glutaric
- Rx low Lys/Try diet, carnitine
- ?child abuse (subdeural hematoma), we do testing to make sure the patient dosen't have Glutaric aciduria type 1

Urea cycle Disorders



Courtesy of Dr. John Walter

The Urea Cycle



Urea cycle defects presentations

- all can present in neonatal period usually they present with high ammonia, with NH3 except arginase deficiency;
- AS lyase deficiency often develop hepatomegaly/fibrosis
- Arginase deficiency – spastic diplegia; IDD
- Lethargy
- Seizures
- Poor feeding
- Tachypnea
- High AMMONIA —> stimulate breathing center —>patient breath a lot—> wash out co2 —>respiratory alkalosis
- Res Alkalosis

Tx

- Restrict protein
- Arginine supp
- IV ammunol (Na benzoate and Na phenylbutyrate)
- Buphenyl (Na phenylbutyrate) – oral powder
- Ravicti (glycerol phenylbutyrate) – liquid
- Liver transplant

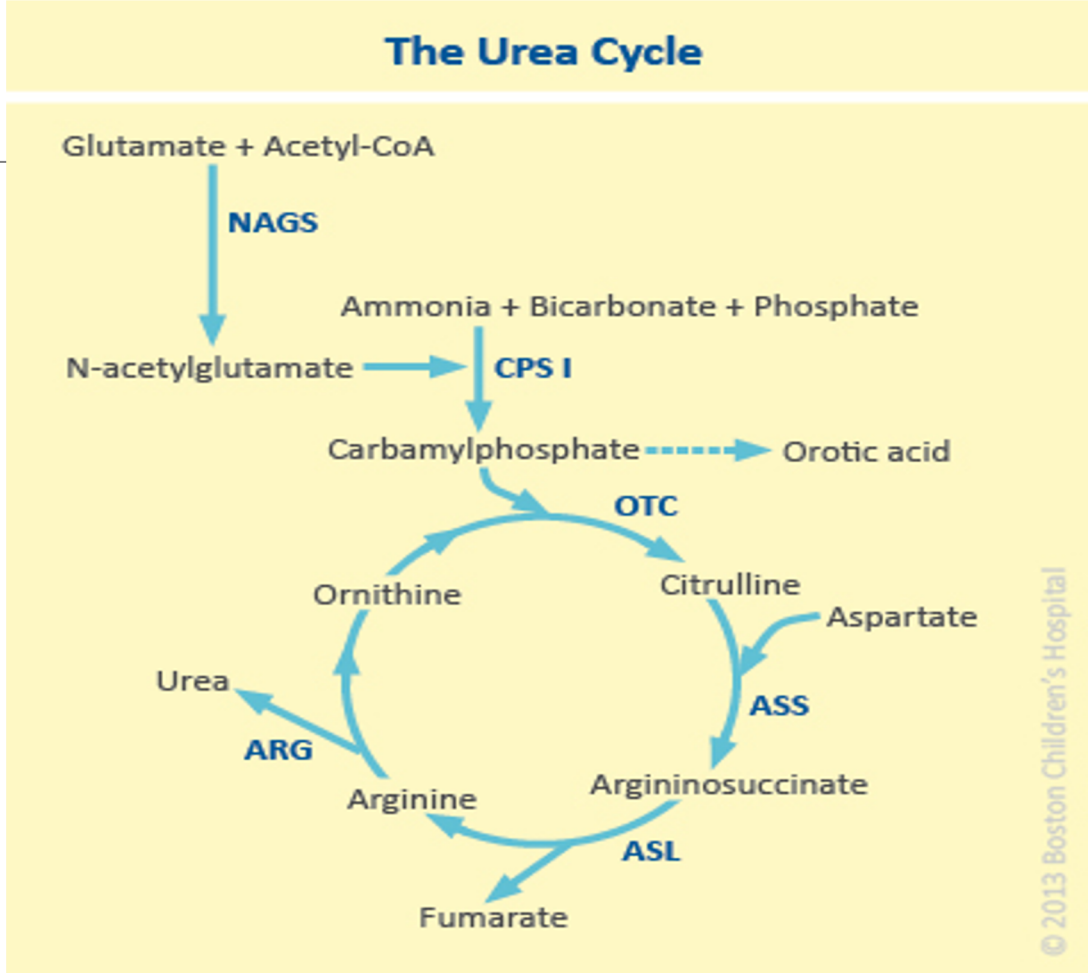
This slide is important

Urea cycle defects Labs

Ornithine transcarbamylase

	OTC dif	Citrullinemia	Arginonosuccinic aciduria
Defect	OTC	ASS	ASL
Citrulline level	LOW	HIGH	HIGH
Arginnosuccinic acid level	LOW	LOW	HIGH
Argenine level	LOW	LOW	LOW
Urine orotic acid	HIGH	NL	NL

Markers help in diagnosis



OTC: Most common urea cycle defect, X-linked inheritance (male)

Organic Acidemeias

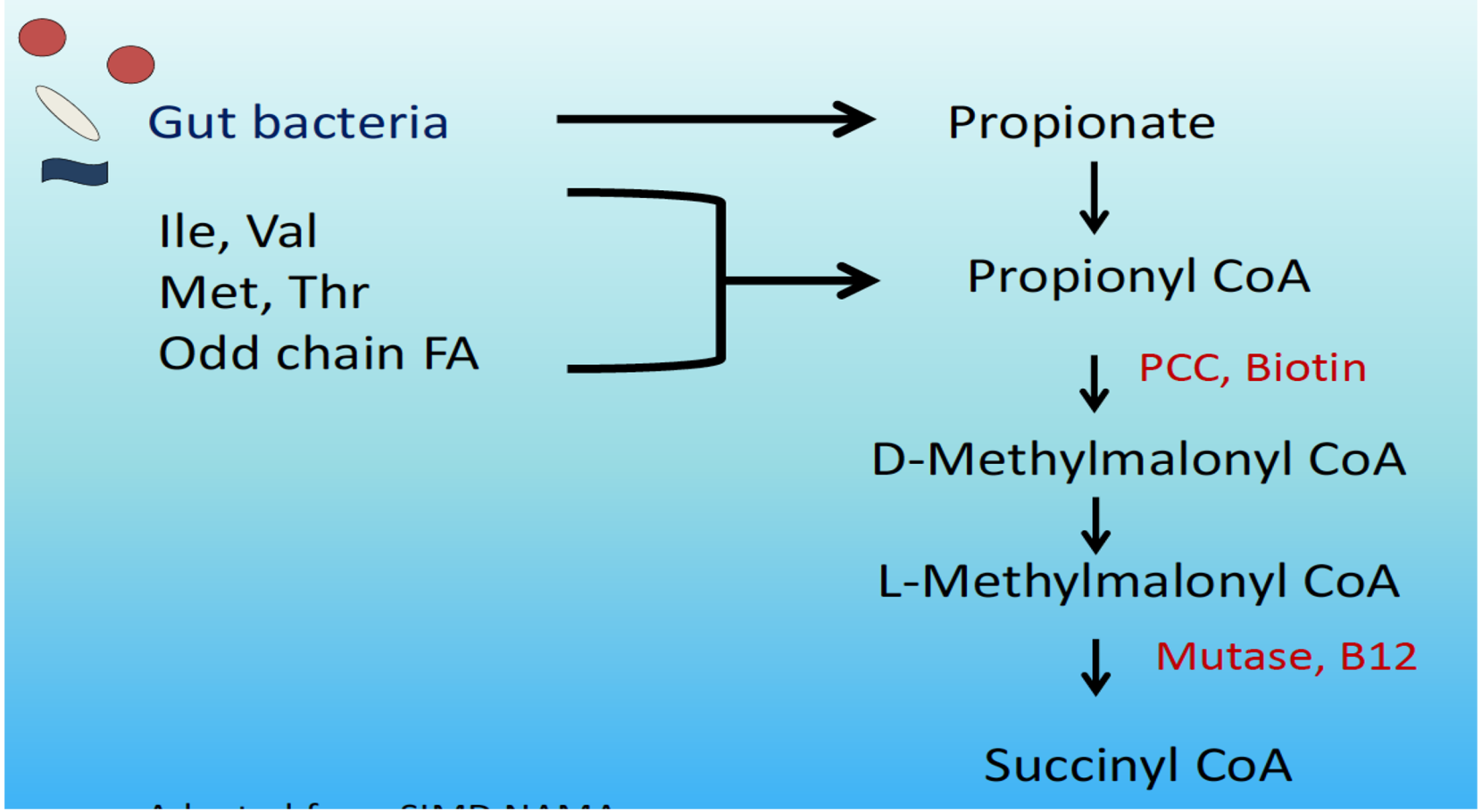
OA

- It is due to deficiency of an enzyme in the branched chain amino acid catabolism.
- Most commonly-
  - Maple syrup urine disease- **maple syrup smell**
  - Isovaleric acidemia– **Sweaty feet smell**
  - Propionic acidemia.
  - Methylmalonic acidemia

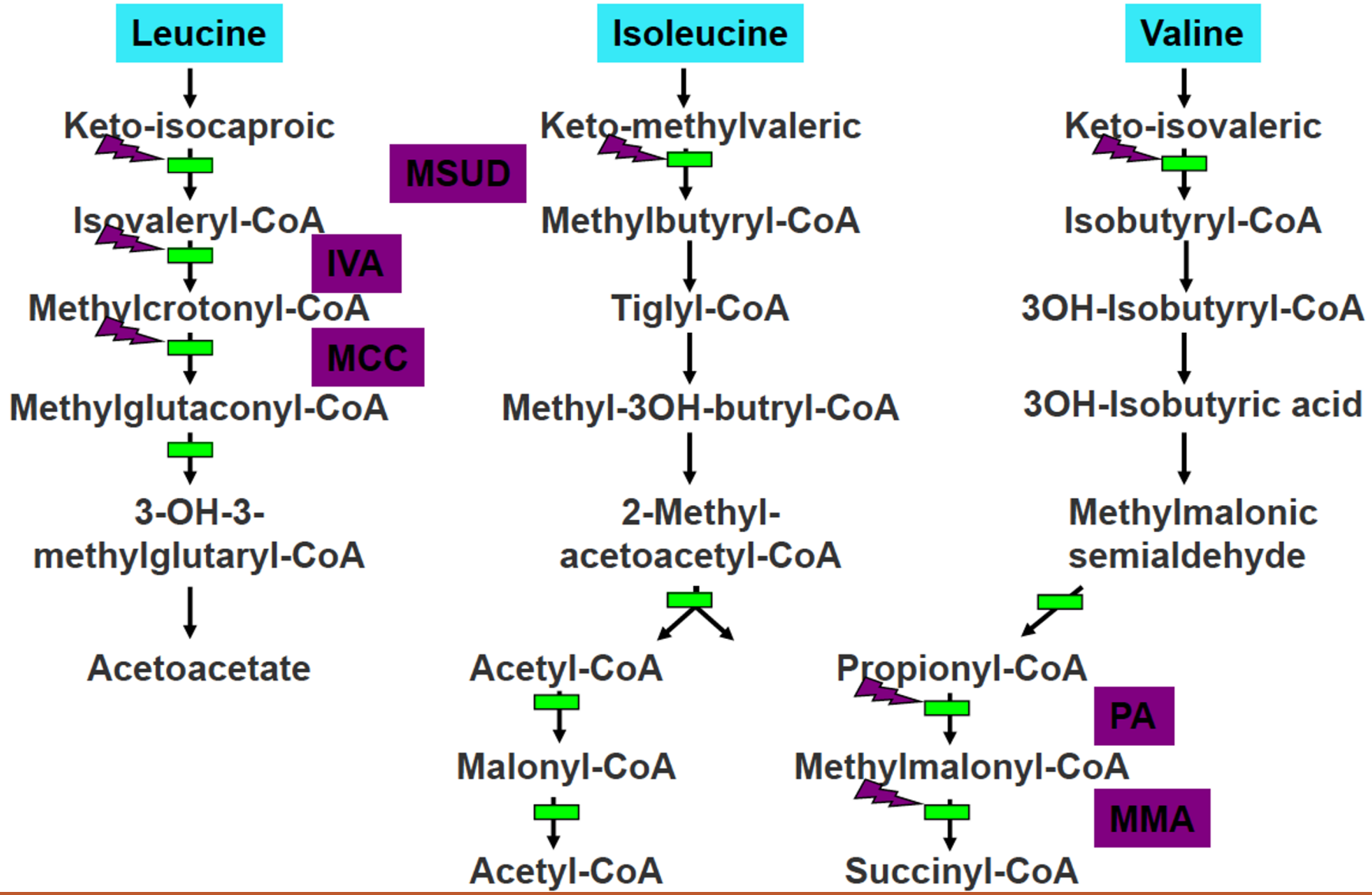
Common is SA

  - Present in infancy with: lethargy, poor feeding, high ammonia, high anion gap metabolic acidosis.to differentiate between OA and urea cycle: OA —> high anion gap metabolic acidosis urea cycle—> resp. Alkalosis
  - Dx- Urine organic acid
  - Treatment- restrict protein, reserve catabolism, lower ammonia

PA and MMA Metabolism



Branch Chain Amino Acid Catabolism



PA and MMA: Some Complications

- Bone marrow suppression during acute crises and as part of chronic disease
- Severe feeding difficulties
- Progressive renal disease
- Cardiomyopathy
- Basal ganglia infarcts
- “metabolic strokes” because of thrombosis
- Pancreatitis
- Eye and vision problems

Treatment of MMA and PA

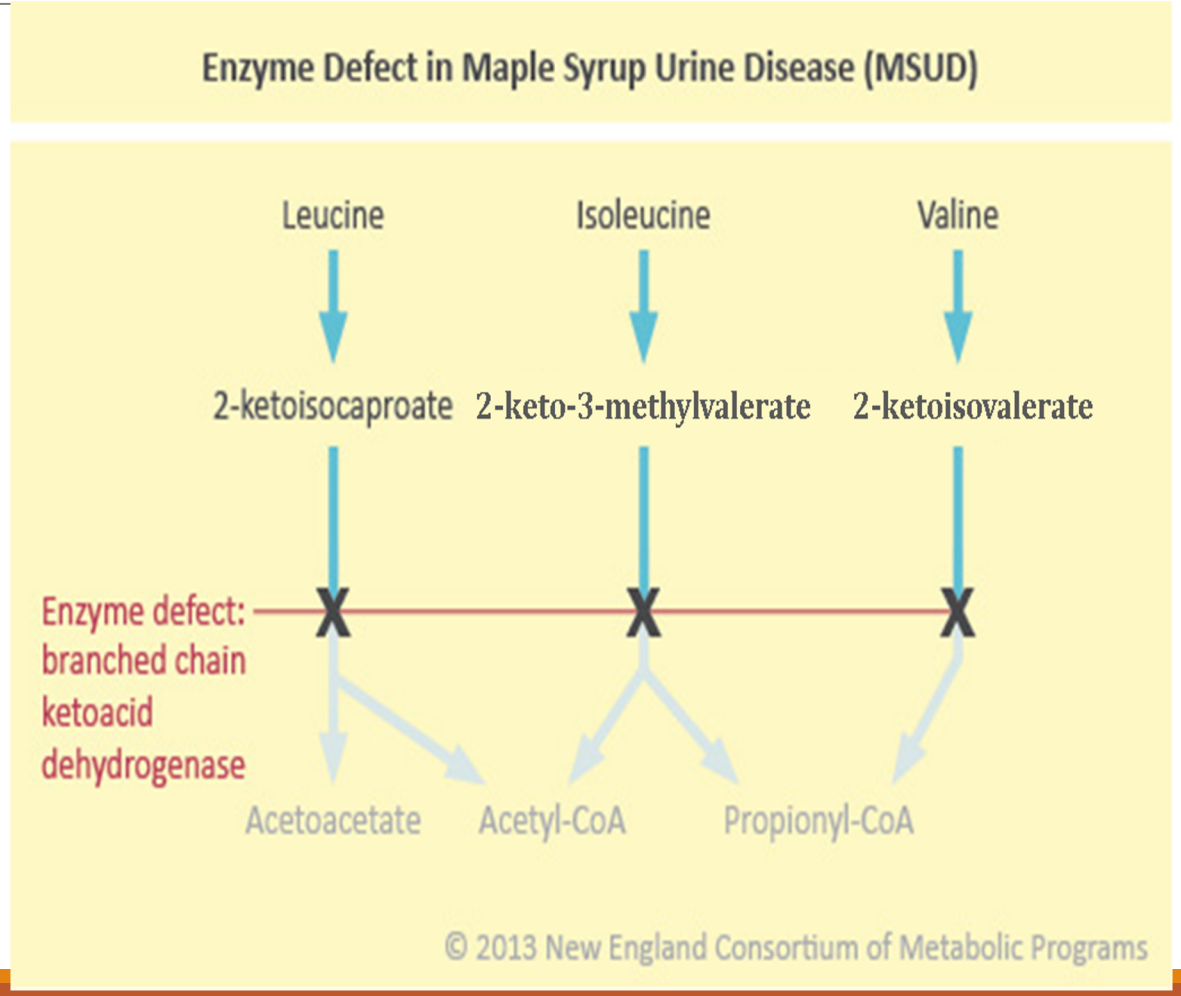
- low protein (Propimex) no need to Remember name
- restrict precursors [Val, Met, Ile, Thr, odd chain FA (VOMIT)]
- carnitine
- biotin
- metronidazole
- carbaglu
- +/- B12

Isovaleric Acidemia (IVA)

- odor of sweaty feet
- UOA: isovaleric & 3 OH isovaleric acid; isovaleryl glycine; ketones
- Rx low protein formula , glycine, carnitine

Maple syrup urine disease (MSUD)

- Branched chain 2-ketoacid dehydrogenase deficiency
- Maple syrup smelling urine
- High valine, isoleucine, alloisoleucine, leucine
- Tx- diet low of branched chain amino acids life long



Not important

Tx of Metabolic Crisis

- CAB
- Stop all source of protein central and parenteral nutrition.
- Check GlucoChecks.
- Insert an IV line and take blood for labs

  - *Ammonia blood sample should be taken with precaution because of high false positive rate (without tourniquet, in green-top tube, put on ice to the laboratory, separated within 20 minutes of collection and analyzed immediately*).

- High caloric intake is the main stay of therapy: 1 1/2 to double maintenance I.V.F as D10 1/2NS + Kcl 30meq/l.

- Keep GlucoChecks 5-8mmol/L.
- Consider start **insulin** if hyperglycemia develop at dose **of 0.01-0.05 unit/kg/hour** and titrate up until blood glucose controlled.
- Increase Carnitine dose to 300-400 mg/kg/day divided Q8 hours IV, orally or NGT.

Do not decrease dextrose rate or amount and DO NOT STOP calorie delivery in the acute stage for any reason as this can precipitate hypoglycemia and catabolism which will further worsen the patient's condition.

Disorders of Carbohydrate Metabolism

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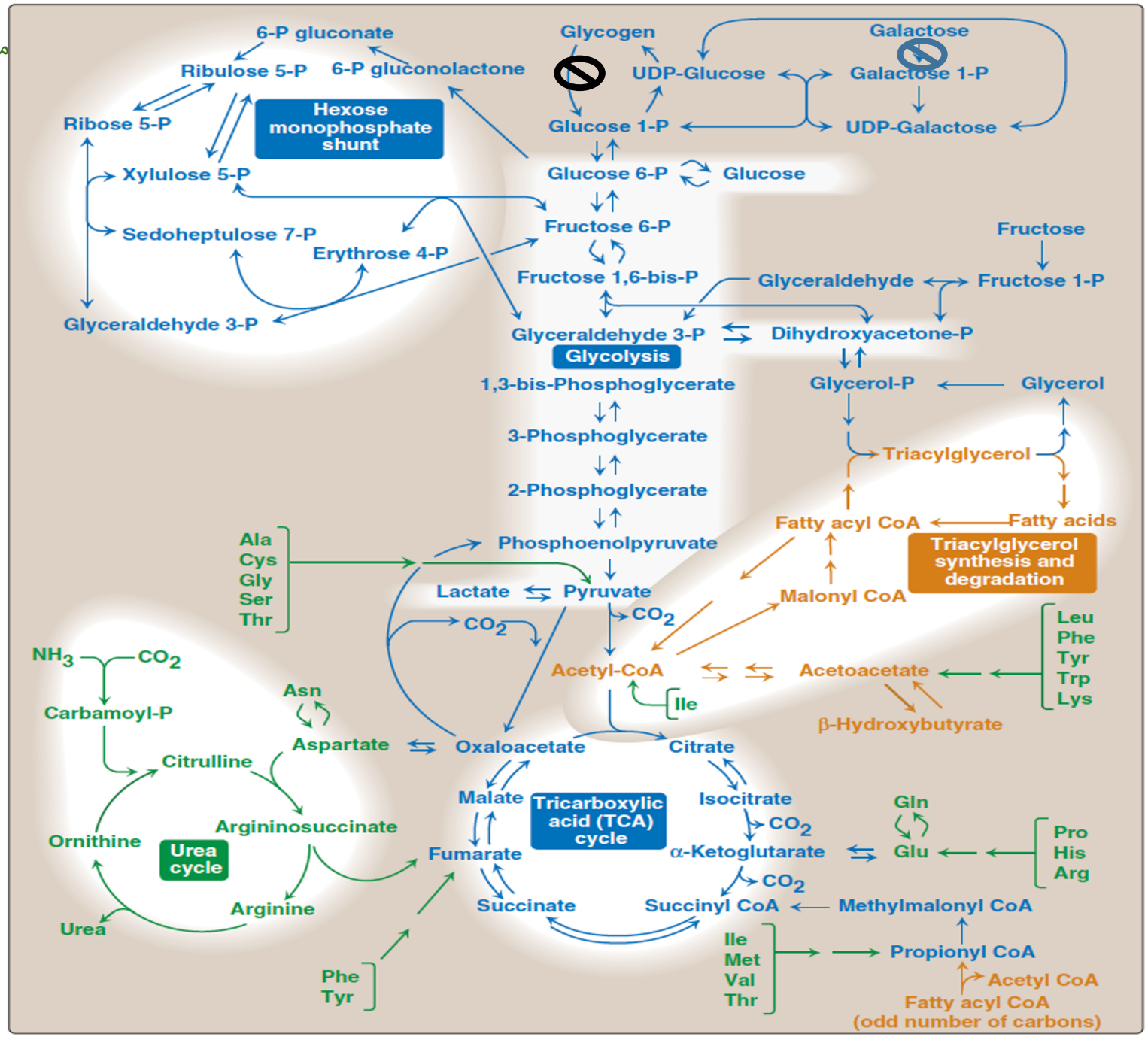
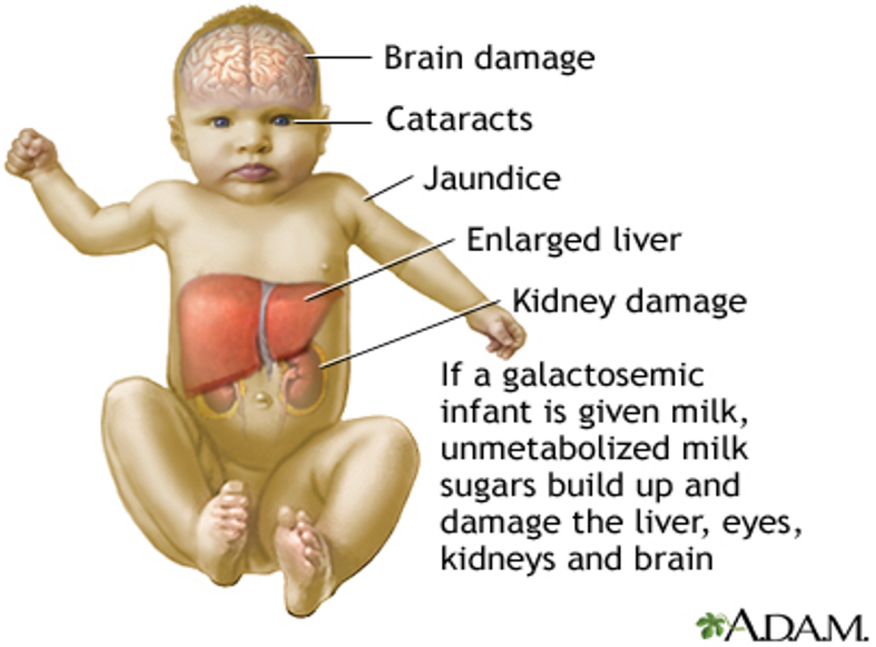
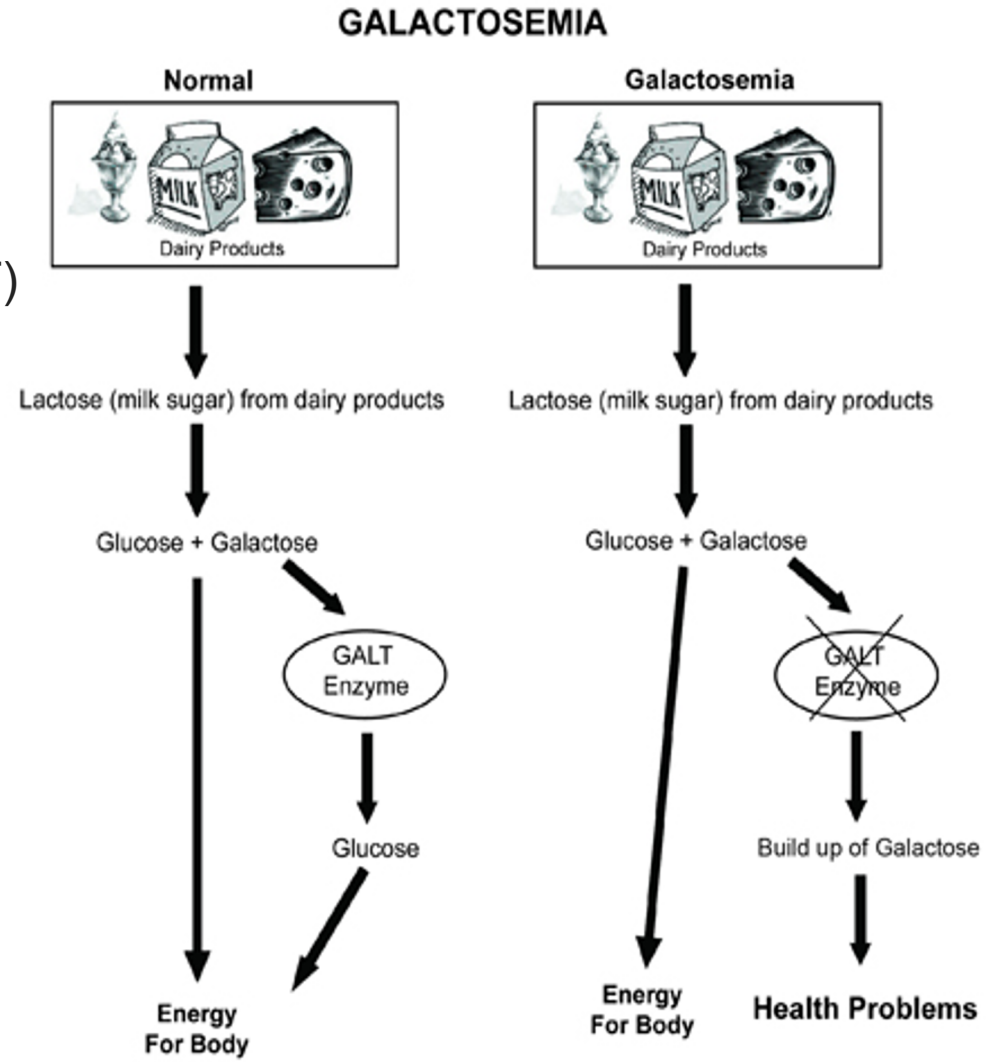


Disorders of:
Glycogenolysis
CHO Utilization

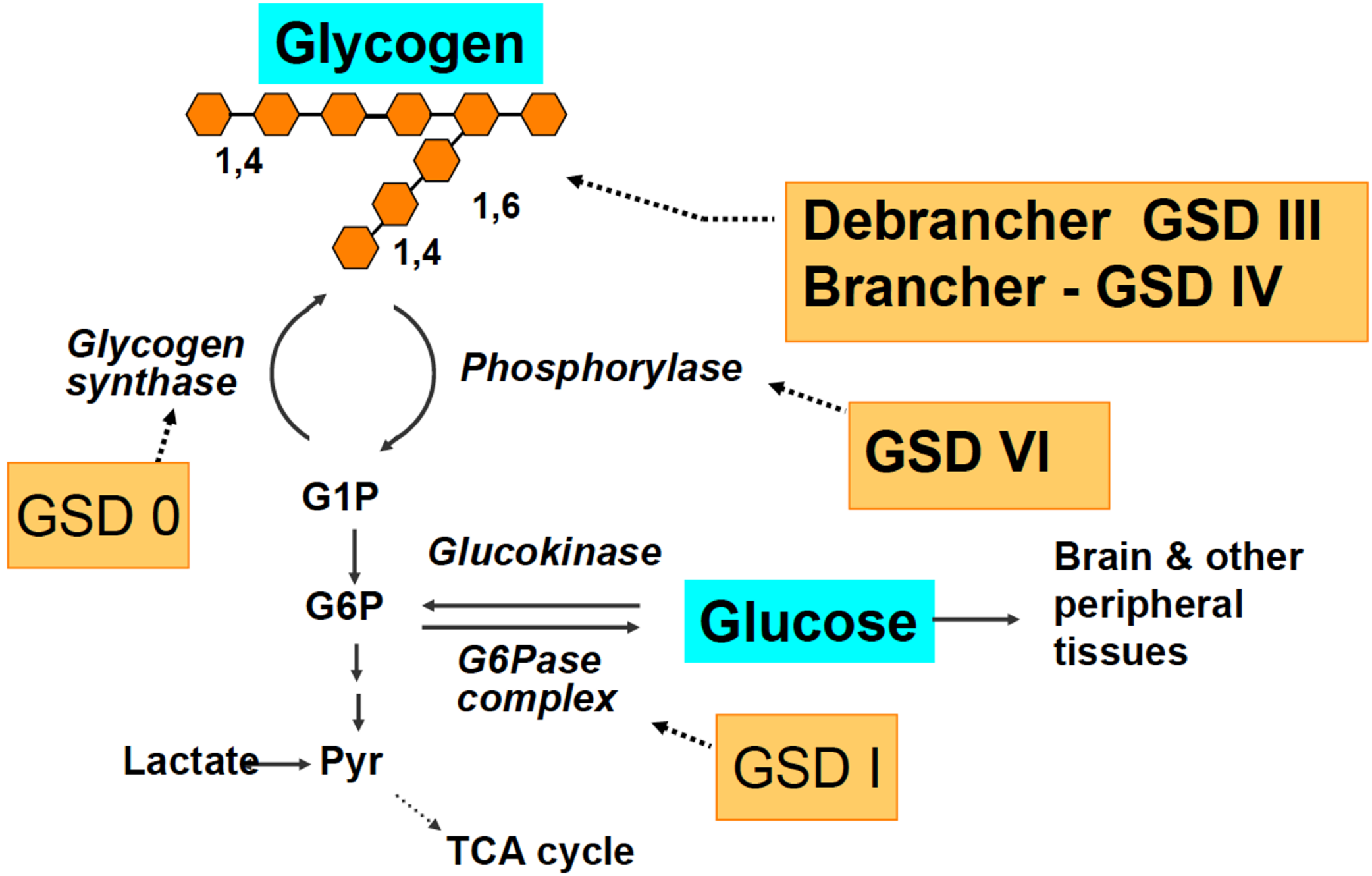
Galactosemia

- Deficiency of Galactose-1-phosphate uridyltransferase (GALT)



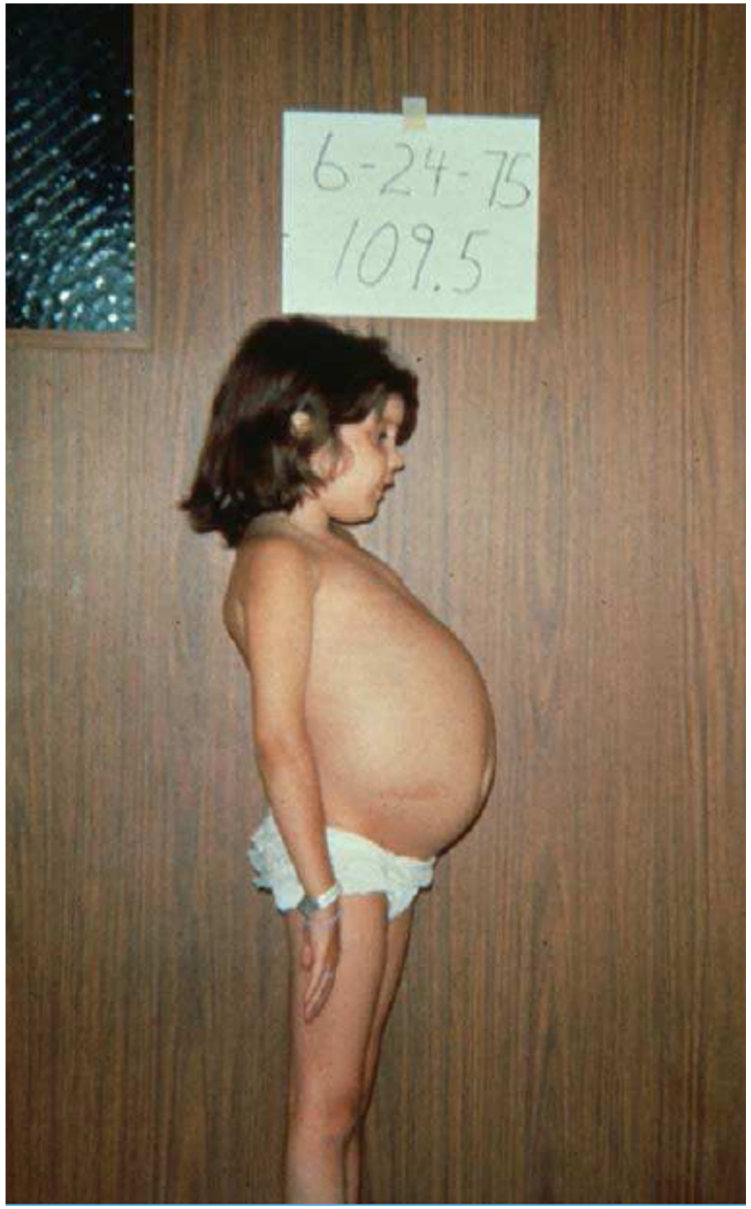


- Treatment: galactose and lactose free diet


Glycogen
1,4
1,6
1,4
Debrancher GSD III
Brancher - GSD IV
Glycogen synthase
Phosphorylase
GSD VI
GSD 0
G1P
Glucokinase
G6P
Glucose
Brain & other peripheral tissues
G6Pase complex
GSD I
Lactate
Pyr
TCA cycle

GSD Ia (Von-Gierke)

- Accumulation of glycogen and fat in the liver and kidneys
- Deficiency of glucose-6-phosphatase (G6Pase) catalytic activity
- Developmental Delay, FTT
- Doll-like faces with fat cheeks, relatively thin extremities,
- short stature, protuberant abdomen, xanthoma and diarrhea
- bleeding tendency with frequent epistaxis.
- chronic neutropenia
- recurrent bacterial infections and oral and intestinal mucosal ulcers.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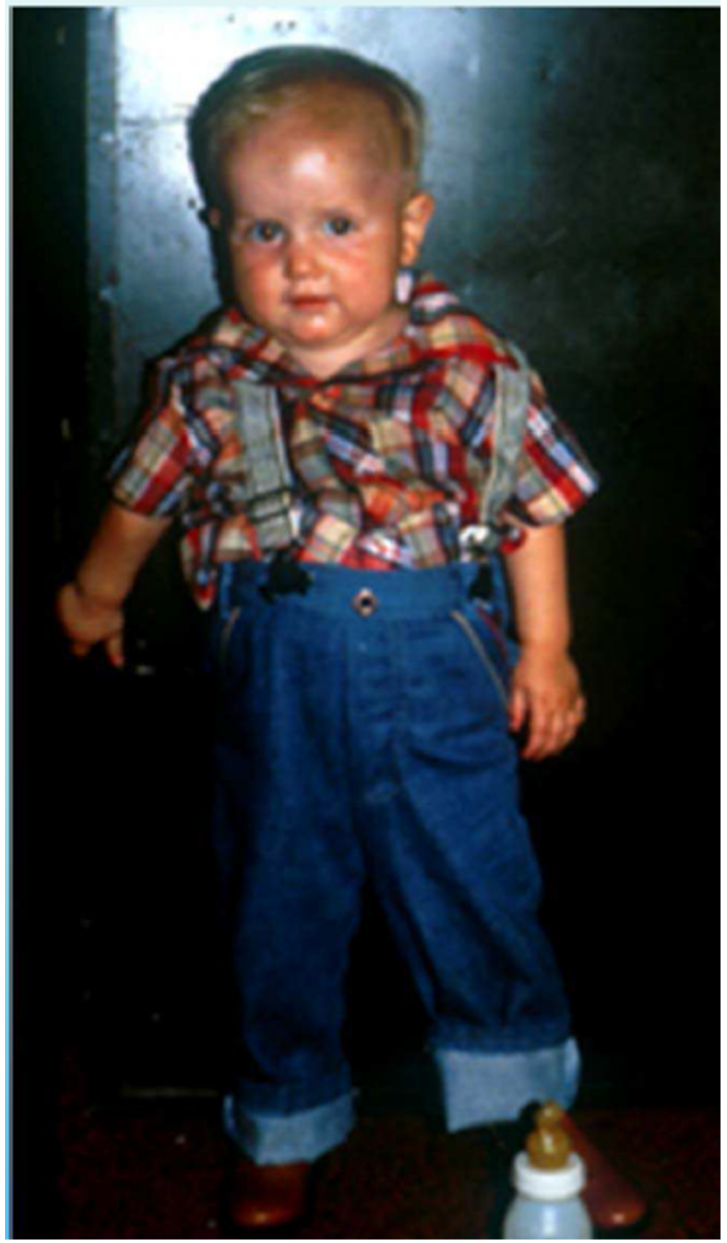
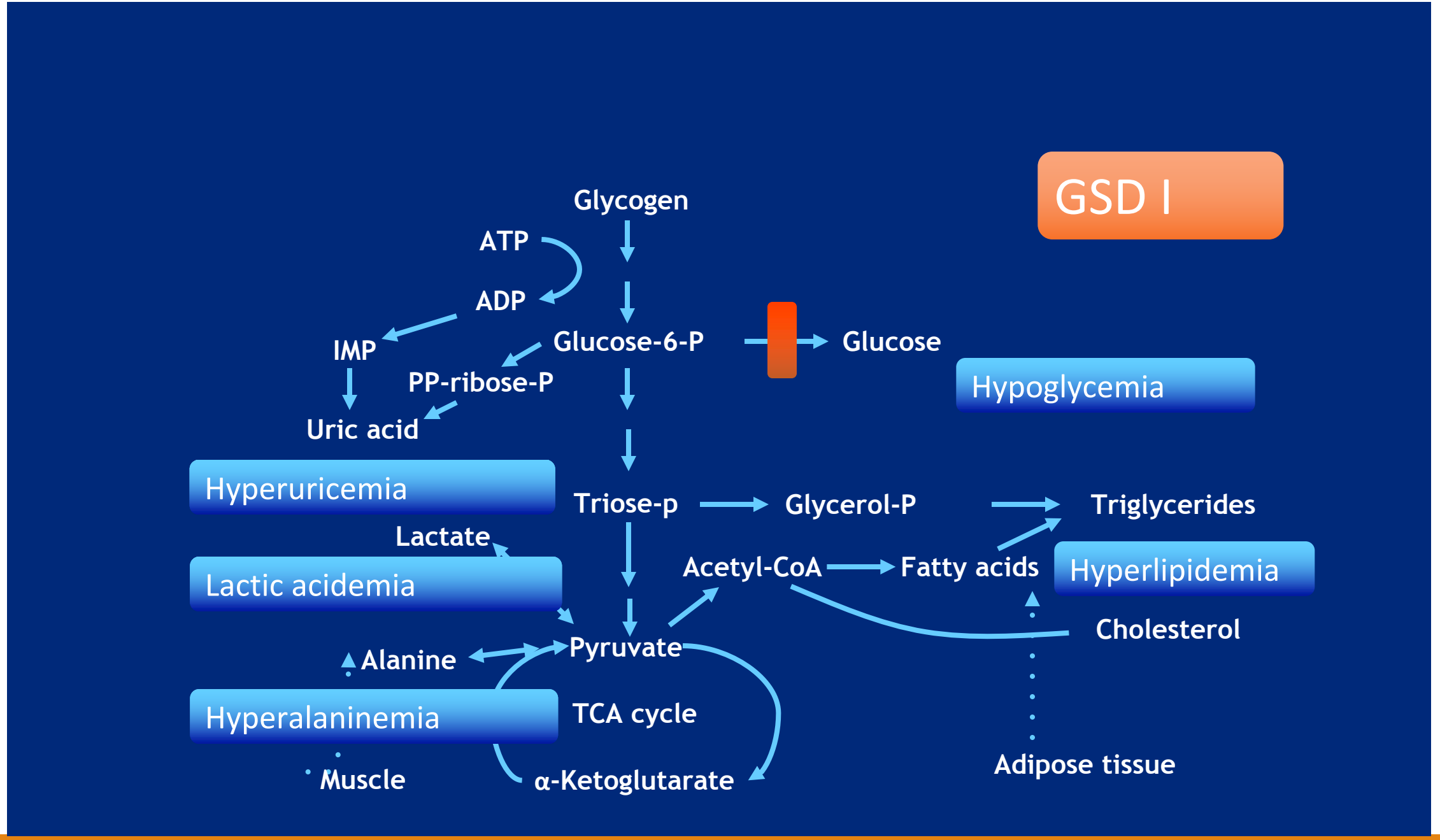



GSD I
Glycogen
ATP
ADP
IMP
Glucose-6-P
Glucose
PP-ribose-P
Uric acid
Hypoglycemia
Hyperuricemia
Triose-p
Glycerol-P
Triglycerides
Lactate
Lactic acidemia
Acetyl-CoA
Fatty acids
Hyperlipidemia
Cholesterol
Pyruvate
Alanine
Hyperalaninemia
TCA cycle
Muscle
α-Ketoglutarate
Adipose tissue

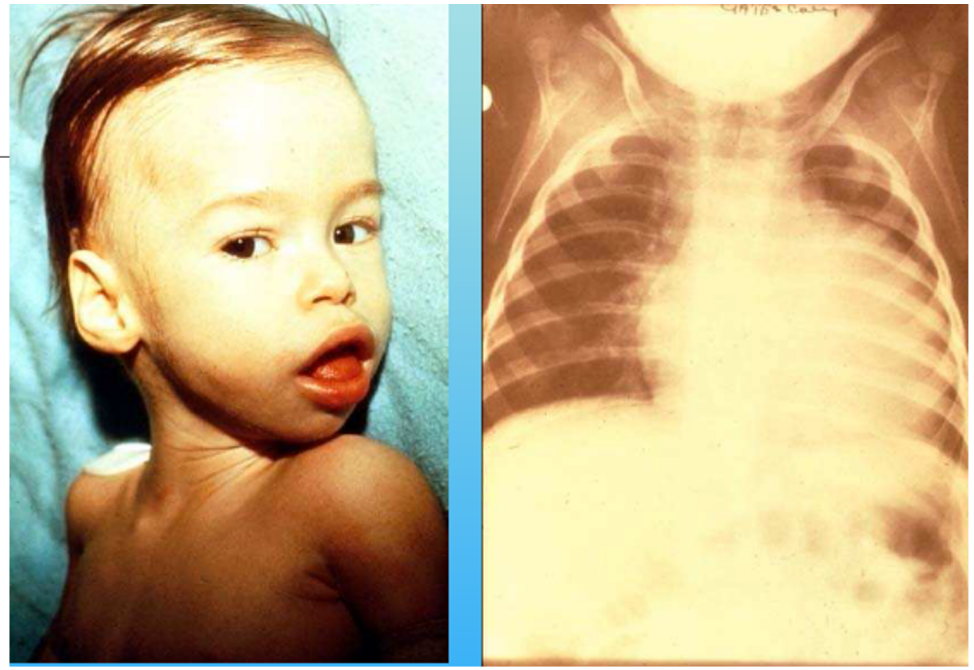
GSD I (Von-Gierke) Treatment

Management:

1. freq. feeds of complex carbs because it's get absorbed slowly.
2. Sucrose (fructose and glucose) and lactose (galactose and glucose) are often limited or avoided
3. Raw cornstarch(complex carbs), between 6 months and 1 year

Pompe disease (GSD II)

Disease of both glycogen storage (mechanism) and lysosomal storage (presentation)



- Lysosomal storage disease
- Alfa glucosidase deficiency
- Glycogen deposits in liver, muscles and heart
- HSM hepatosplenomegaly
- Hypertrophic cardiomyopathy, cardiomegaly
- Hypotonia
- FTT
- Macroglossia big tongue
- NO hypoglycemia because other glycogen stores can be broken down ,problem just in the heart's glycogen
- Treatment- Enzyme replacement therapy

مو لازم تحفظوه

Table 21.1 Glycogen-storage diseases

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen	Branching enzyme (α-1,4 ⟶ α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.

Table 21.1
***Biochemistry*, Seventh Edition**

Lysosomal Storage Diseases

Introduction

- Lysosomes cytoplasmic organelles that contain ~50 acidic degradative enzymes
- Deficiency results in accumulation of macromolecules usually degraded by that enzyme/protein.
- Stored material may cause enlargement of organs and may be visualized in membrane bound vesicles by EM
- Target organs affected by each disease are determined by normal sites of degradation of each compound
- Most patients are normal at birth; as material accumulates there is a plateau and then regression

Types

- MPS Mucopolysaccharidosis

- oligosaccharaidosis

- sphingolipidosis: GM1 ganglosidosis, GM2 ganglosidosis (Tay-Sachs/Sandhoff), NPC, Gaucher, Fabry

- Mucolipidosis

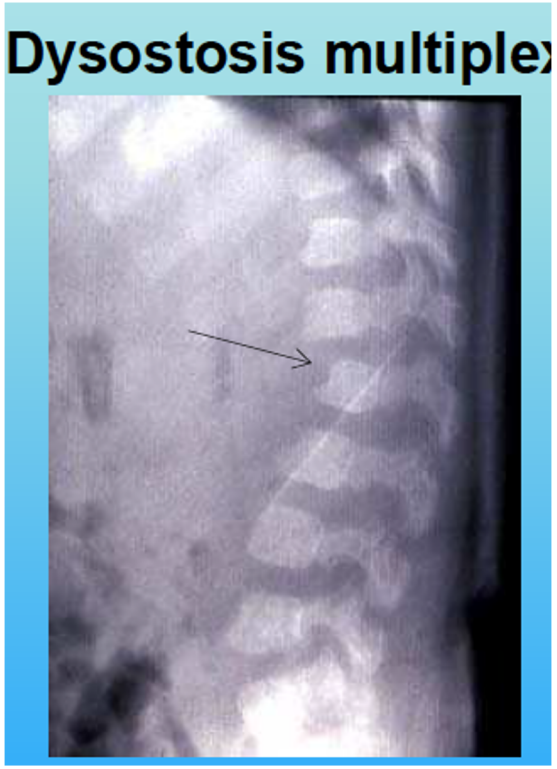
- Lipid Storage

- Neuronal ceroid lipofuscinoses

- GSD

Some General Phenotypic Features

- Coarse facies
- Organomegaly (liver, spleen)
- Eye abnormalities: Corneal clouding, Cherry red spot, Optic atrophy, Pigmentary retinopathy
- Skeletal abnormalities
- Non immune hydrops

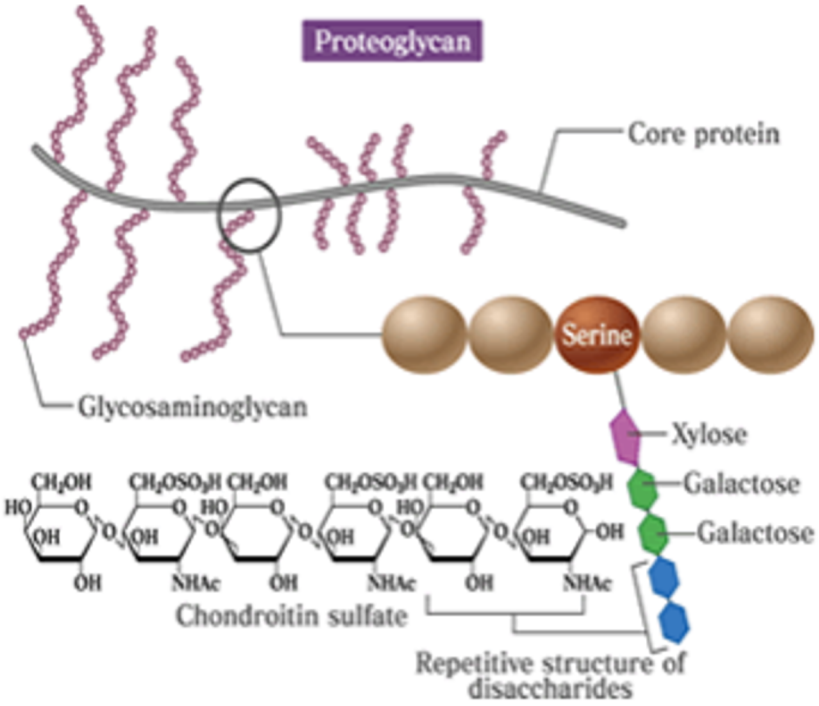


General Diagnostic Approach

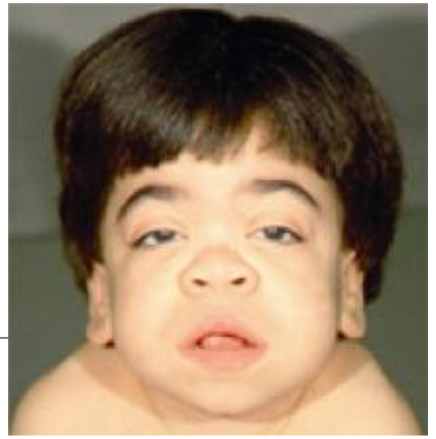
- Serum lysosomal enzymes
- Blood smear
- Radiologic exam
- Ophthalmologic exam fundoscopic and slit lamp
- Urine mucopolysaccharides and glycoproteins
- Consider bone marrow
- Biochemical studies of fibroblast +/ leukocytes
- Molecular/gene sequencing

Mucopolysaccharidoses (MPS)

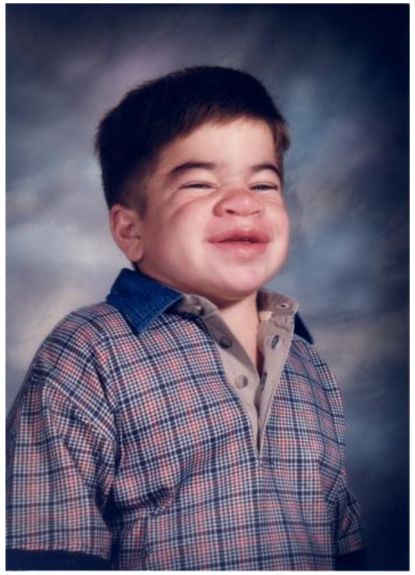
- Defect lysosomal enzyme needing to break down glycosaminoglycans
- Progressive
- Coarse features, thick eye brows, organomegaly, contractures, growth deceleration, deafness
- Dysostosis multiplex on x ray
- Hearing loss (sensorineural & conductive)
- Recurrent herniae, thickened mucous membrane
- Late cardiac involvement
- All autosomal recessive except hunter



MPS features



- Hurler (MPS I)- Growth deceleration, **corneal clouding**, HSM, pes cavus, hirsutisim
- HUNTER (MPS II)- skeletal anomalies, NO corneal clouding الصياد لازم يشوف بعيد عشان كذا عيونه كويسه
- SAN FILLIPO (MPS III)- behavioral problems
- MORQUIO (MPS IV)- normal IQ, skeletal involvement

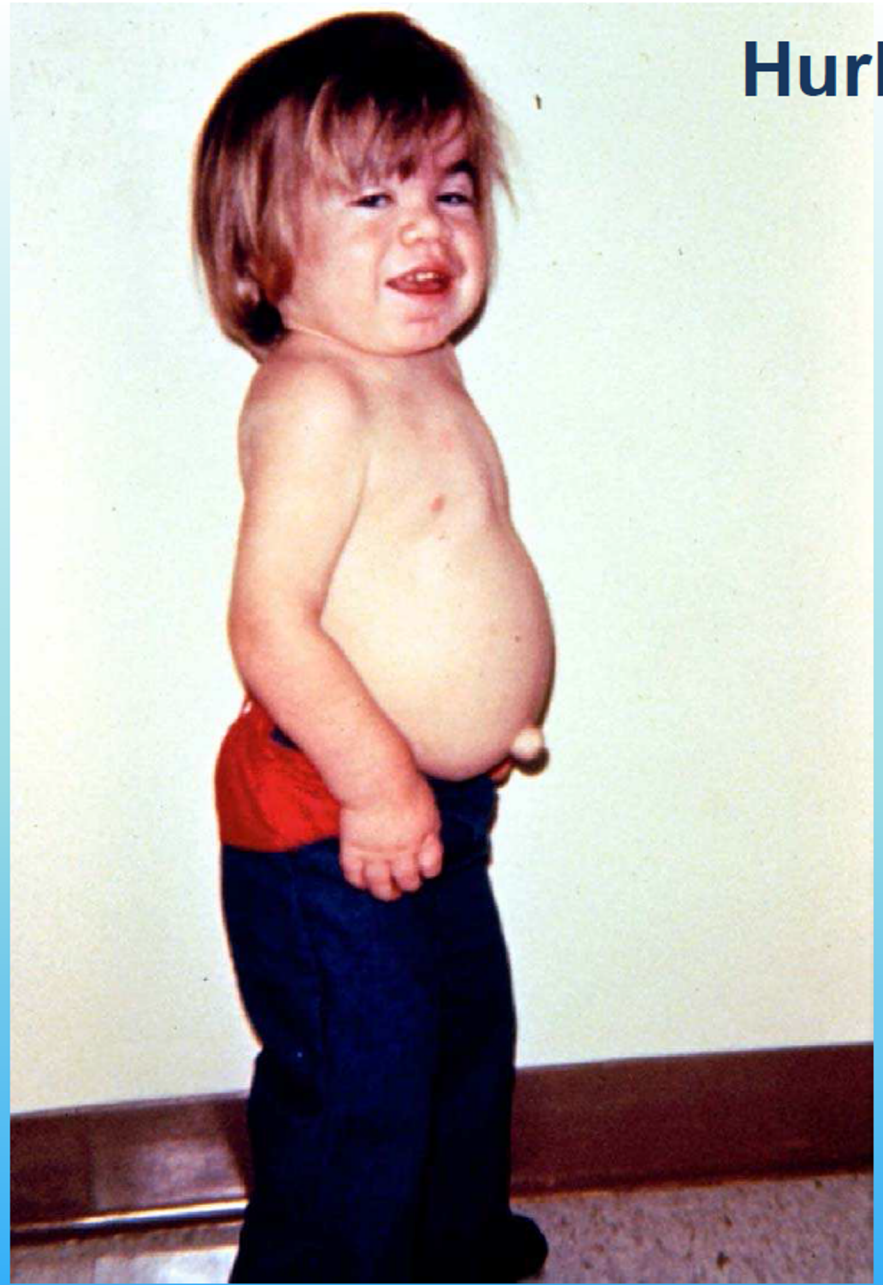


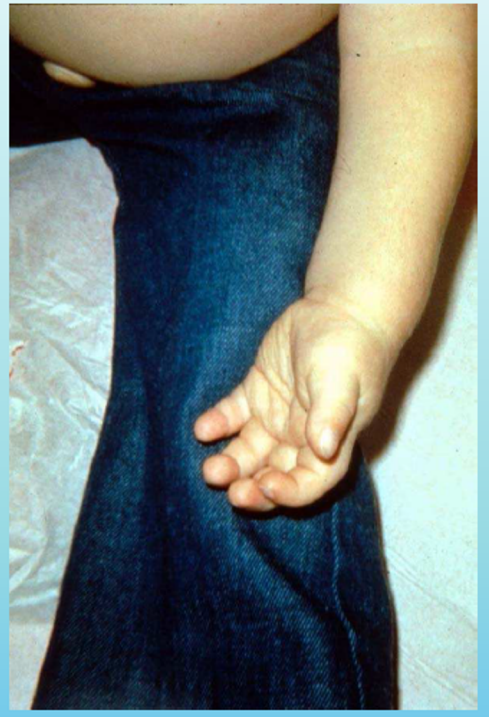
- Treatment: HSCT, Enzyme replacement therapy for treatment
- In Some cases we do bone marrow transplant but outcome not very good

Other Features of MPS Disorders

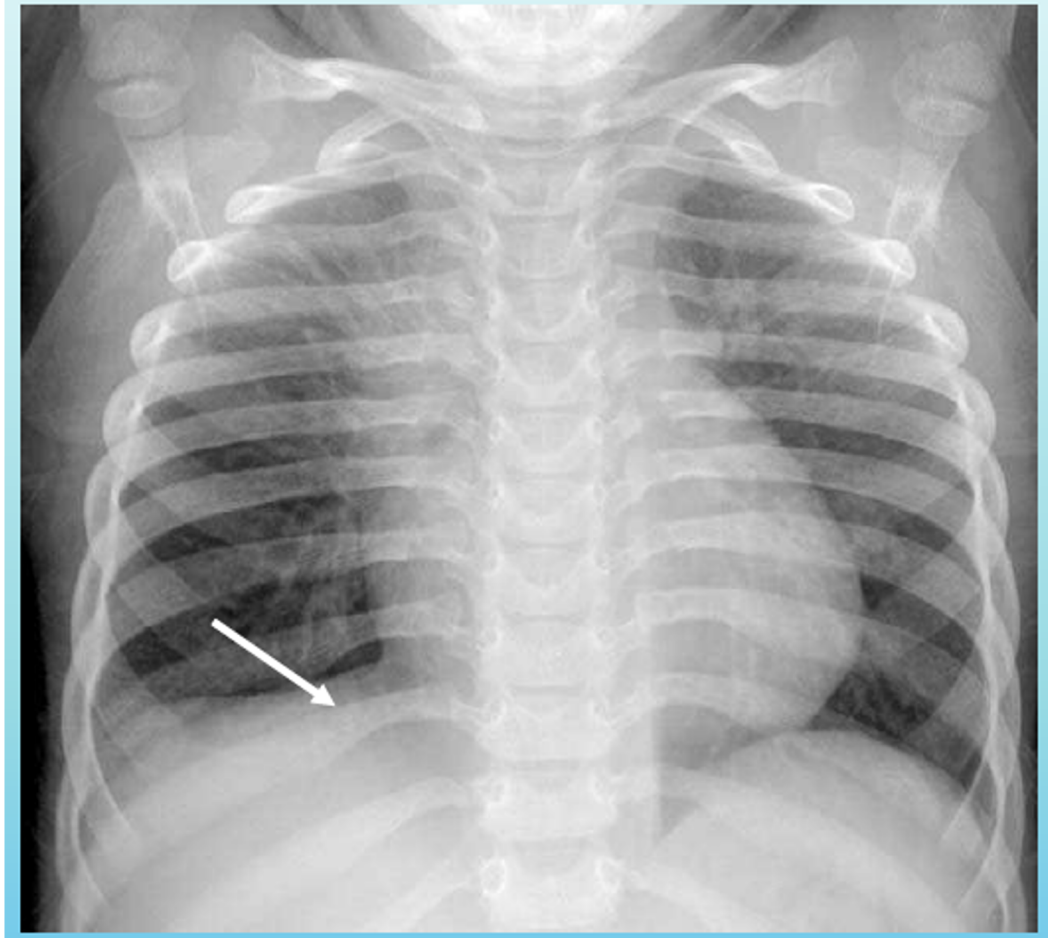
- Hydrocephalus
- Obstructive airway disease; difficulty with intubation; excessive secretions
- Atlantoaxial instability; odontoid hypoplasia
- Cardiac disease valvular, conduction disturbances, cardiomyopathy
- Pulmonary and systemic hypertension

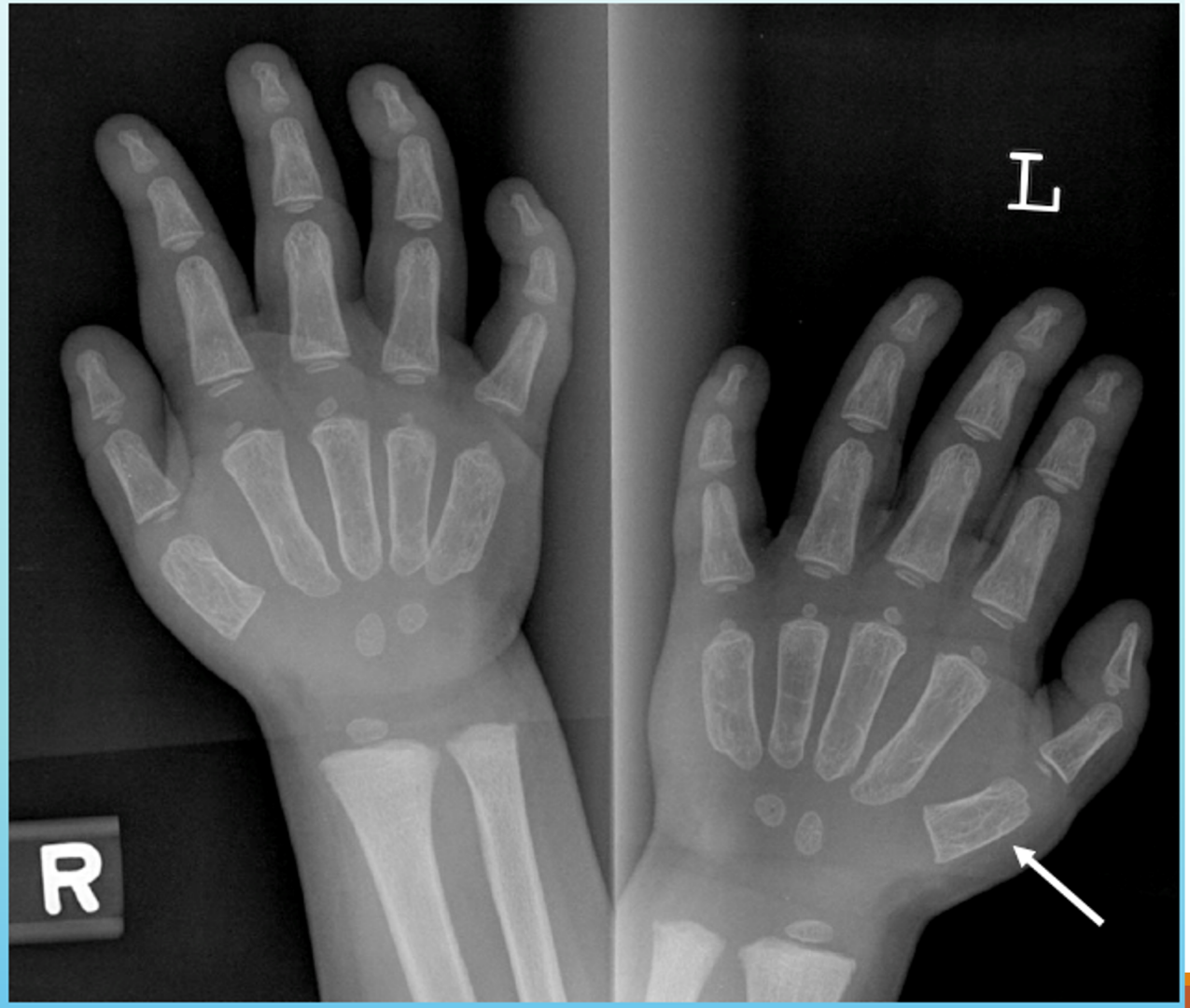
Hurler Syndrome





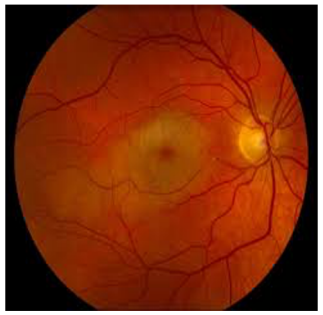
Dysostosis Multiplex





GM2 Gangliosidosis Very sad disease

- Tay Sachs more common in Jewish , Sandhoff more common in Arabs
- Def. hexosaminidase A/B enzyme
- Progressive neurological deficits
- Normal till 9 months then show developmental regression
- Hypotonia , Macrocephaly
- **Exaggerated startle response** لما يسمع البيبي صوت عالي يفز فزه قويه بعكس البيبي الطبيعي
- **Cherry red spots**
- No organomegaly
- Die early
- Ashkenzi jews
- No treatment

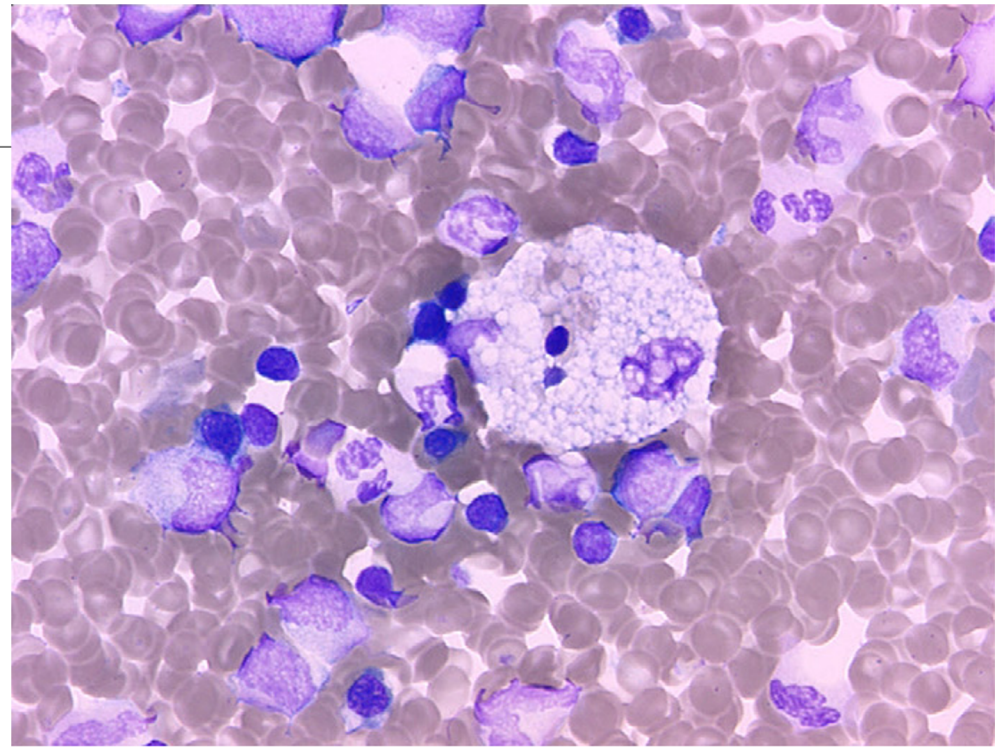


Niemann-pick A, B

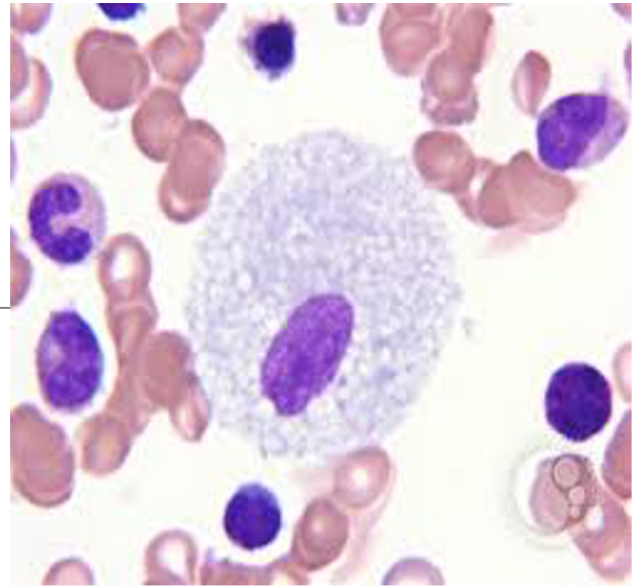
- Sphingomyelinase def.
- CNS problems – hypotonia
- HSM (vs. Tay Sachs) no HSM in Tay Sachs
- Cherry red spots
- Interstitial lung disease
- Death by 4 years
- Dx- foam cells (Niemann Pick cells) in bone marrow
- No treatment

Niemann Pick C

- Disorder of cholesterol trafficking—> cholesterol storage
- Juvenile: ataxia, speech delay, HSM, progressive intellectual decline, dystonia
- Adult onset- ataxia, dystonia, psychiatric, hepatomegaly
- Dx- foam cells (Niemann Pick cells) in bone marrow now we do genetic testicular instead
- Tx- miglustat



Gaucher`s disease



- Dif. Beta-glucocerebrosidase enzyme

  3 types based on clinical symptoms

- Type I nonneuronopathic; splenomegaly, pancytopenia, bone pain/lytic bone lesions

  Type II acute neuronopathic rapidly progressive neurologic disease with hepato splenomegaly

- Type III subacute neuronopathic later onset

  Dx “foam macropahes” in bone marrow, smear; enzyme assay

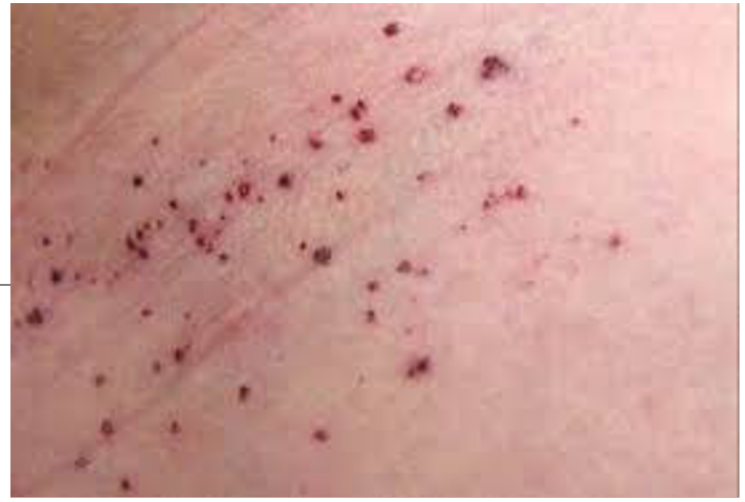
  Treatment- Rx symptomatic; splenectomy; ERT for Type I pts (no effect Type II)

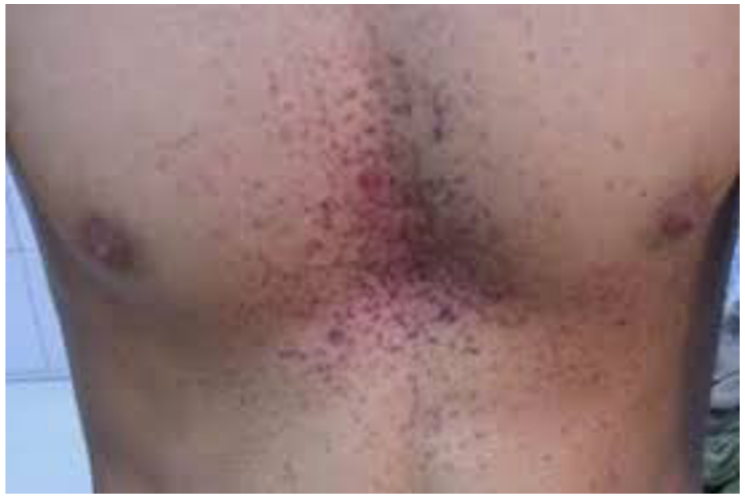
Doctor skipped this slide

Fabry Disease

Very rare

- X linked
- males– median age of onset 9 yrs; peripheral neuropathy; acroparesthesias;mangiokeratomas; lens/corneal opacities; late : renal and cardiovascular disease; chr lung disease with fibrosis
- Accounts for ~1% chr renal failure & 5% cryptogenic stroke; incidence cardiac variant
- Most females have sx – median age of onset 13 yrs; fatigue, stroke, ~10% females develop renal failure
- Tx- ERT





Cherry Red Spot Manifest in :

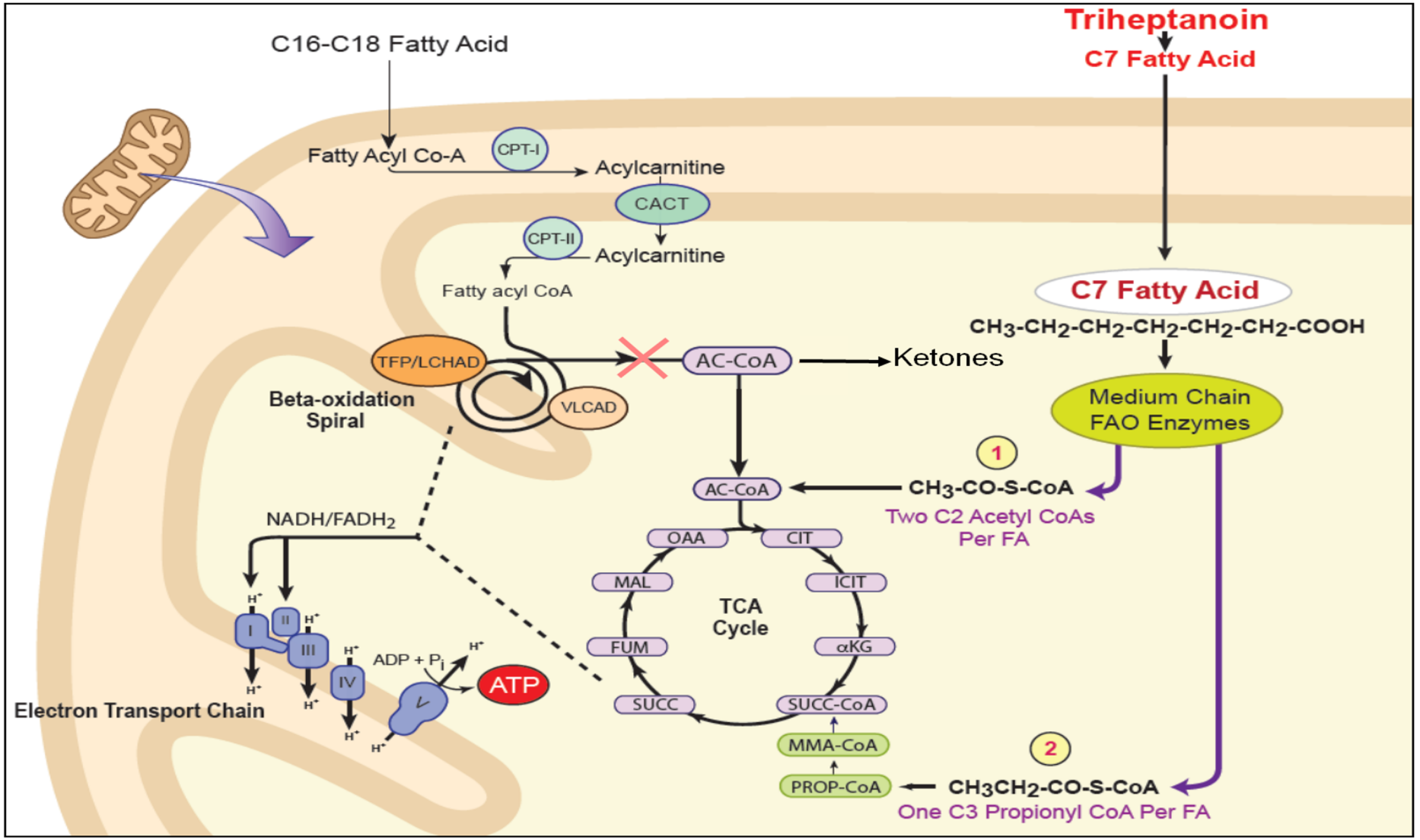
- Tay Sachs Disease
- Sandhoff Disease
- Sialidase deficiency (mucolipidosis type 1)
- Niemann Pick Disease Type A
- GM1 Gangliosidosis

Foam Cells” in Bone Marrow

Most of lysosomal diseases show foam cell that’s why is not good way to diagnose. We do genetic test to know the type.

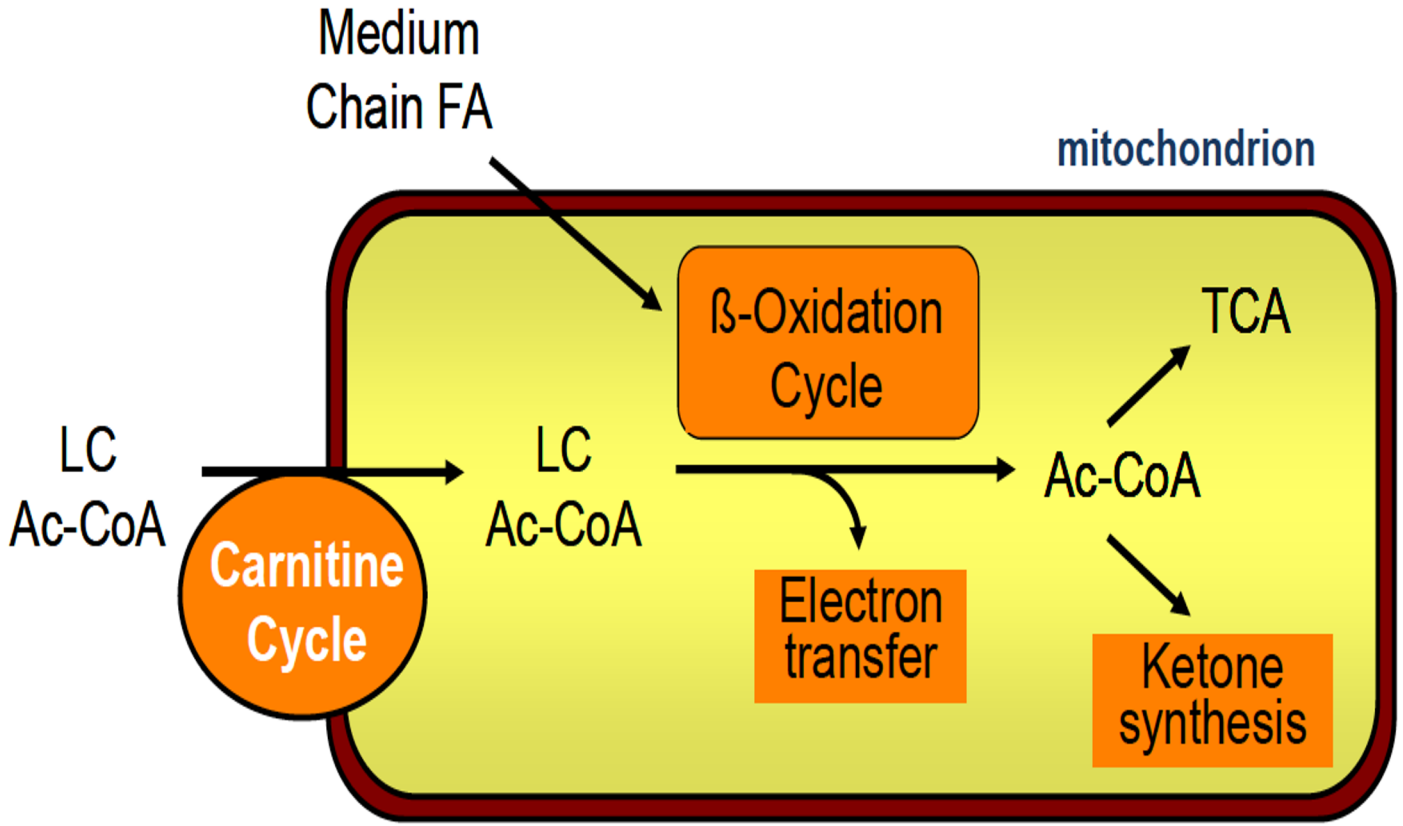
- Neimann–Pick disease (types A, B, C, D)
- G_{m1} gangliosidosis (type 1)
- G_{m2} gangliosidosis (Sandhoff variant)
- Mucolipidosis
- Fucosidosis
- Mannosidosis
- Neuronal ceroid-lipofuscinosis
- Chronic hyperlipidemia
- Chronic corticosteroid therapy
- Hematologic malignancies (e.g., Hodgkin disease, leukemia, myeloma)
- Hematologic disease (e.g., aplastic anemia, ITP).

Fatty Acid Oxidation


Triheptanoin
C7 Fatty Acid
C16-C18 Fatty Acid
Fatty Acyl Co-A
CPT-I
Acylcarnitine
CACT
CPT-II
Acylcarnitine
Fatty acyl CoA
C7 Fatty Acid
CH3-CH2-CH2-CH2-CH2-CH2-COOH
TFP/LCHAD
AC-CoA
Ketones
VLCAD
Beta-oxidation Spiral
Medium Chain FAO Enzymes
1
AC-CoA
CH3-CO-S-CoA
Two C2 Acetyl CoAs Per FA
NADH/FADH2
OAA
CIT
MAL
ICIT
TCA Cycle
FUM
αKG
SUCC
SUCC-CoA
MMA-CoA
2
PROP-CoA
CH3CH2-CO-S-CoA
One C3 Propionyl CoA Per FA
I
II
III
IV
ADP + Pi
ATP
Electron Transport Chain

- During fasting FAO provides up to 80% total body energy needs
- Long chain (LC) fats preferred substrate for cardiac and skeletal muscle
- LC free fatty acids (FA; C18, C16) released from TG in adipose tissue
- Peripheral tissues oxidize FA to CO2 and H2O Liver oxidizes FA to ketone bodies for energy for gluconeogenesis and ureagenesis
- Ketone bodies used as fuel in CNS

Doctor skipped this slide



Four components of fatty acid oxidation:

- Carnitine cycle
- ß-oxidation cycle
- Electron transfer
- Ketone body synthesis

FAO

- Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
- Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD)
- Very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD)

No need to remember these long name

- Baby presents with **Non-ketotic hypoglycemia**, high ammonia, high CK, liver involvement, cardiomegaly

- Treatment- low fat formula

S/S

- coagulopathy
- enlarged liver, fasting intolerance
- Cardiac cardiomyopathy, arrhythmias
- Sudden death liver (hypoglycemia),
- Acute rhabdomyolysis
- Chronic – weakness, fatigue, lactic acidosis
- Risk HELLP (hemolytic anemia with elevated LFTs and ow platelets) in females with LCHAD fetus

Summary of the lecture

If you don't have time just read this table اغلب الاسئلة تجي من هذا الجدول ا

Disorder	Glucose	NH3	Ketones	Acidosis	Note
Organic acidemia	LOW	HIGH (usually)	++	High AG met acidosis	- Early DOL2 -thrombocytopenia, pancytopenia, neutropenia -dehydration (PA, MMA) -IVA (sweaty feet)
Urea cycle	NL	HIGHHH	NO	NO	-Hypotonia -tacypnea
FAO	LOW	NL/HIGH (prot. Breakdown)	NO	NO	- + stress, illness, fasting - Nonketotic hypoglycemia - Hepatomegaly
GSD I (von Gierk)	LOW	NL	++	High AG met acidosis	- Pt cant breakdown glycogen. They dep on fats, prot, anarobic metabolism - HSM, doll-faces - High uric acid
Amino acidopathy	Nl	Nl	NO	NO	- PKU (mousy odor, light color skin), alkaptonuria (black urine), Homocystinuria (marfanoid, clots)
Galactosemia	LOW	NL	NO	NO	- 1st wk, vomiting, diarrhea, sz, jaundice, HSM, **cataract**, DD -Galactose deposit in kidney, liver, brain -Increase risk f gram negative sepsis (E.coli)

Question

Question

A two-week-old female infant presents with a several day history of lethargy and poor feeding, with repeated vomiting. The infant was a product of a normal pregnancy and an uneventful vaginal delivery.

Birth weight was 3810 gm; today's weight is 3520 gm. The infant is jaundiced, and has a weak, high-pitched cry. The liver edge is palpable 2 cm below the right costal margin.

Complete blood count is unremarkable. Total indirect (unconjugated) bilirubin is elevated. Urine is positive for reducing substances (means there is galactose in the urine) when tested by the clinitest method, although a standard urinalysis is unremarkable. Blood glucose is 42 mg/dl (low) . Which of the following is the most likely diagnosis?

1. Sepsis may present with lethargy and poor feeding but without unconjugated bilirubin nor reducing substances
2. Subdural hematoma no Hx of trauma
3. Formula intolerance
4. Neonatal hepatitis not sudden,conjugated high bilirubin ,no hypoglycemia
5. Galactosemia

a 7-day-old male infant; he was born at term. He is the 3.5 kg product of an uncomplicated pregnancy, labor and unassisted vaginal delivery of a 27-year-old g_2p_1ab0 woman; the patient presents with the sudden onset of vomiting, lethargy, and tachypnea. He is bottle-fed and was feeding vigorously until today. He has had no fever, rhinorrhea, cough, diarrhea, or abdominal distention. An older sister had the onset of similar symptoms at 5 ½ years of age, as did their mother, in both of whom these symptoms would recur episodically, usually with an intercurrent infection. A maternal uncle died in infancy with very similar symptoms; he also experienced seizures. Examination reveals a normal temperature, a pulse of 134, a blood pressure of 88/52 mm hg, and a respiratory rate of 62. He is lethargic. The anterior fontanelle is slightly sunken. There is mild skin tenting and moderate hypertonia. The lungs are clear. There is no organomegaly or petechiae. You obtain blood, urine, and cerebrospinal fluid cultures, all of which are pending. Cerebrospinal fluid cell count, glucose, and protein are normal. Chest radiography is normal. An arterial ammonia level is 1,650 mcg/dl (high). Ketones are normal.

For exam purpose —> x-linked disease happen in male only
In real life X-linked disease can present in female but in very mild form

what type of disorder best accounts for this patient's clinical picture?

1. UCD
2. Aminoacidopathy
3. OA
4. FAO
5. Lysosomal storage

Case

You are asked to evaluate a 4-day-old male infant; he was born at term. He is the 3.1 kg product of an uncomplicated pregnancy, labor, and unassisted vaginal delivery of a 24-year-old $g_1p_0ab_0$ woman. There was a positive newborn screening test for phenylketonuria (PKU). The child's mother reports that he appears to be completely well; he has been breast feeding without difficulty or vomiting. Physical examination is entirely normal.

Question

what would you tell this child's mother?

1. Most positive results are FP, need to repeat screen in 2 weeks
2. Since child is feeding well, no need for further evaluation
3. He child need to start immediately on phe- restricted diet
4. Most positive results are true positive, so most likely your son has PKU
5. He child needs plasma phe and tyrosine level

To confirm the diagnosis because the screening test could be false positive.

Questions??