The Annual General Pediatric Review & Self Assessment

Nicklaus Children's Hospital

METABOLISM

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OVERVIEW OF METABOLIC DISORDERS

- Classification
- Clinical presentation
- Newborn screen
- Common metabolic disorders
- Principles of treatment

CLINICAL PRESENTATION

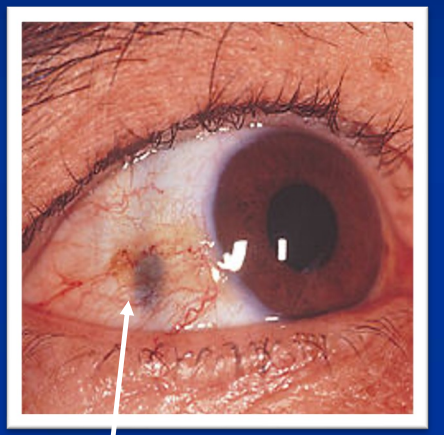
- Overwhelming illness in the neonatal period
- Vomiting (?pyloric stenosis)
- Acute acidosis, anion gap (ORGANIC ACIDEMIA)
- Massive ketosis
- Hypoglycemia (FATTY ACID OXIDATION DEFECTS, HYPERINSULINISM)
- Coagulopathy
- Coma
- Seizures, especially myoclonic
- Chronic hiccups (NON KETOTIC HYPERGLYCINEMIA)
- Unusual odor (MSUD)
- Extensive dermatosis (especially monilial)
- Family history of siblings dying early

URINE AND BODY ODORS

Odour	*Disorder/Origin*
Mouse	PKU
Maple syrup	Maple syrup urine disease
Sweaty feet	Isovaleric aciduria,
Cat urine	3-Methylcrotonylglycinuria,
Cabbage	Tyrosinaemia type I,
Rancid butter	Tyrosinaemia type I
Acidic	Methylmalonic acidaemia
Sulphur	Cystinuria
Rotten fish	Trimethylaminuria,

URINE COLOR

COLOR	SUBSTANCE	DISORDER
BROWN	MET-HB	MYOGLOBINURIA
BLUE	INDICAL	HARTNUP
RED	RBC, RED BEET, PORPHYRINS	HEMATURIA, FOOD, PORPHYRIA
BROWN	HOMOGENTISATE	ALKAPTONURIA



Ochronosis

SPECIFIC TRIGGERS OF METABOLIC DECOMPENSATION

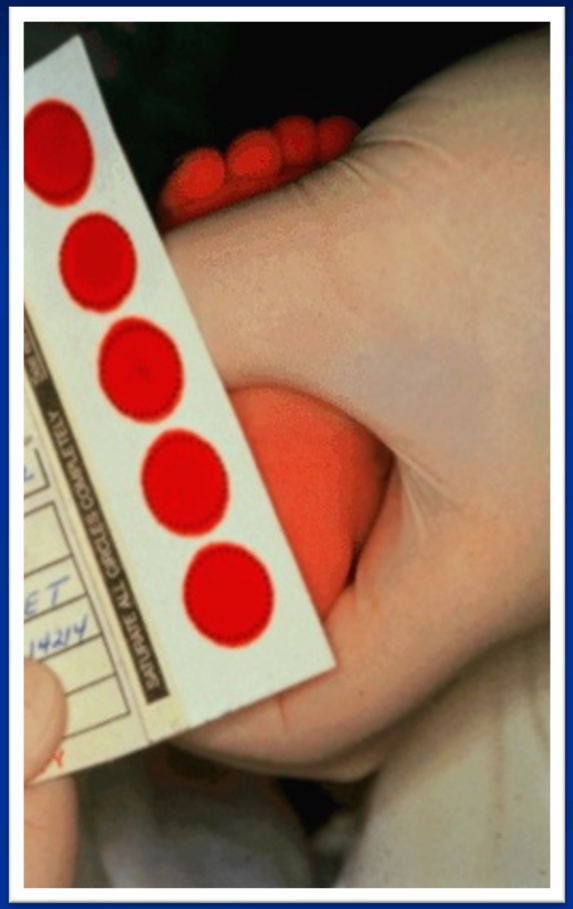
Triggers	*Groups of disorders*
Fasting, infections, fever, vaccinations, operations, accidents	Disorders of protein, energy and carbohydrate metabolism
High protein intake and/or protein catabolism	Disorders of protein metabolism: aminoacidaemias, organic acidurias, urea cycle defects
Fruit, table sugar (sucrose)	Fructose intolerance
Lactose, milk products	Galactosaemia
High fat intake	Fatty acid oxidation disorders,
Drugs	Porphyrias, Glc-6-P-dehydrogenase deficiency, fatty acid oxidation disorders

LABORATORY SCREENING TESTS

- Lactate
- Ammonia
- Plasma Amino Acids
- Urinary Organic Acids /Urine Acylglycines
- Acylcarnitine Profile
- Carnitine
- Biotinidase

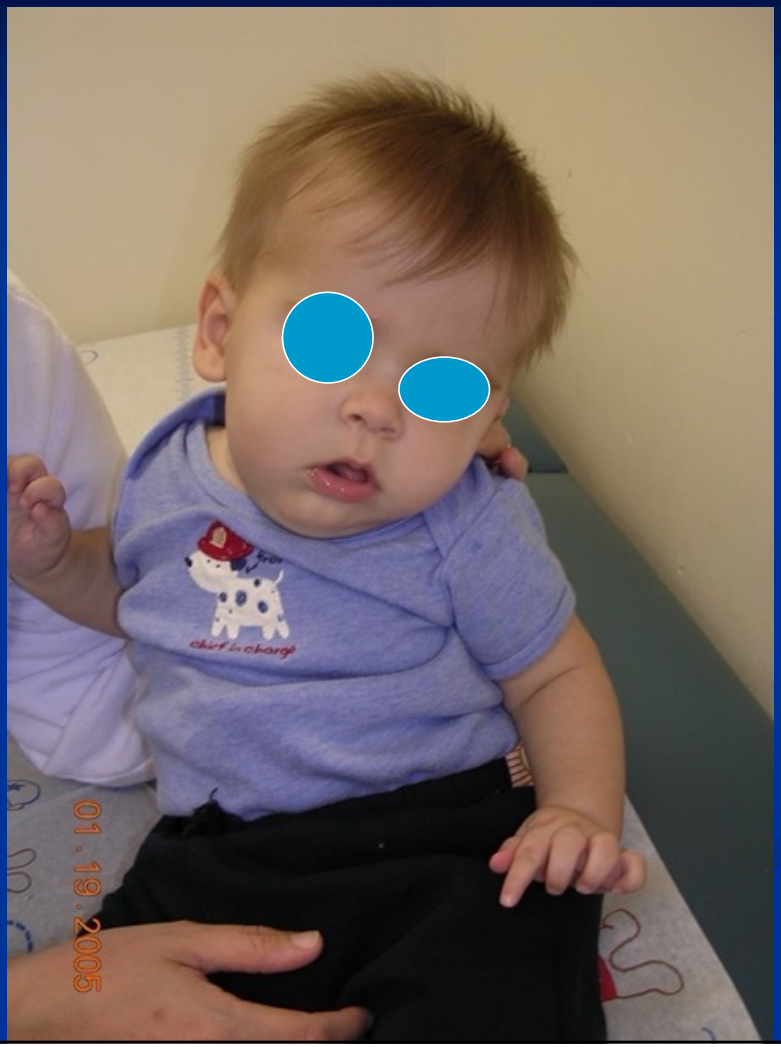
EXPANDED NEWBORN SCREENING

- Detect presymptomatic
- Reduce mortality/morbidity



NORMAL DEVELOPMENT
AT 5 MONTHS

NEUROREGRESSION
DX'ed WITH GLUTARIC ACIDURIA 1

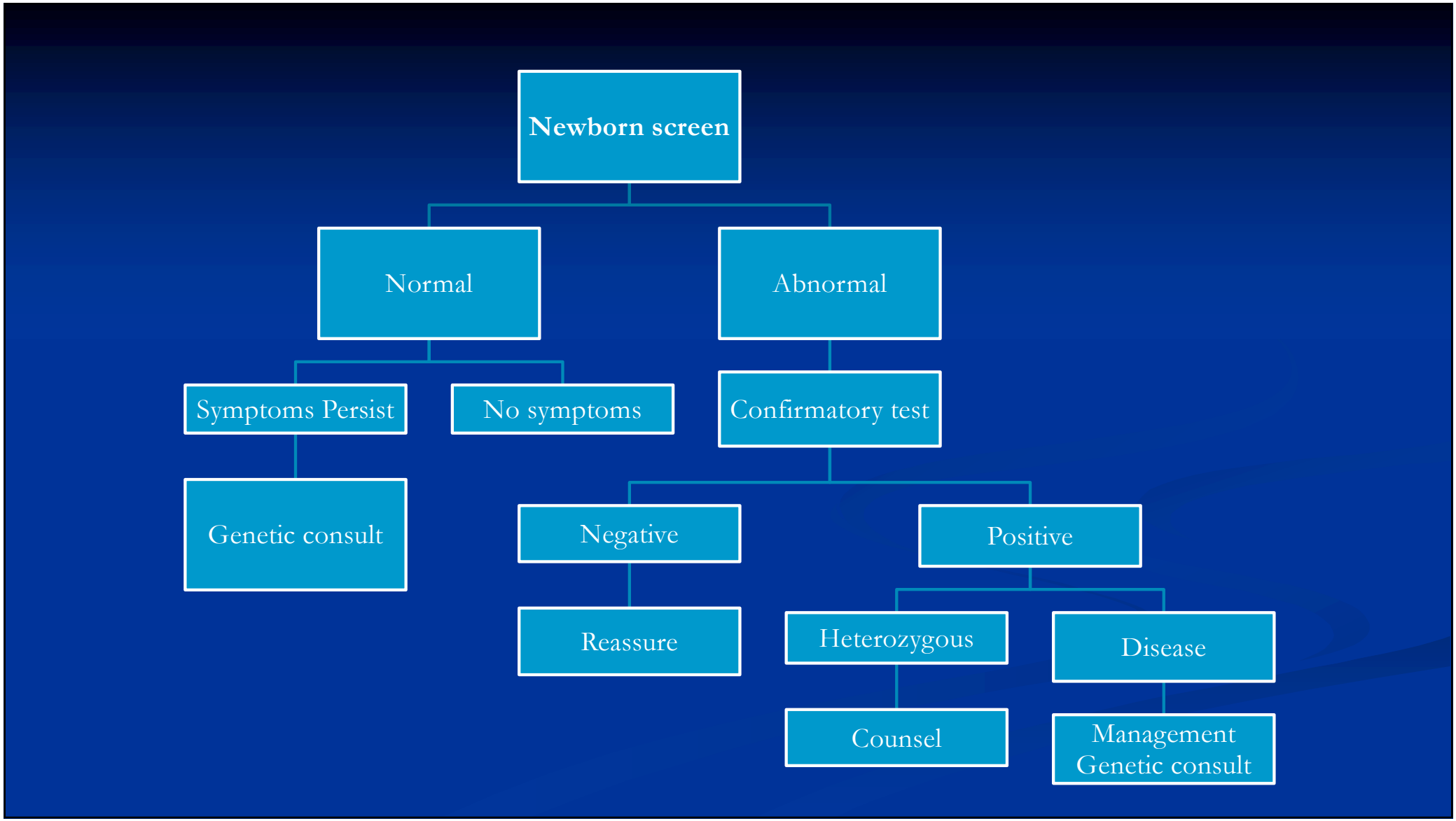


DISORDERS RECOMMENDED FOR NEWBORN SCREENING USING TANDEM MASS SPECTROMETRY

- Amino acidemias
  - PKU
  - MSUD
  - HCY
  - ASA
  - Citrulinemia
  - Tyrosinemia I and II
- Organic Acidemias
  - PA
  - IVA
  - 3-MCCD
  - HMG
  - SKAT
  - GA 1
  - MMA
  - MCD
- Fatty acid oxidation defects
  - Carnitine metabolism (CAT, CUD, CPTI and II)
  - SCAD
  - GAII/MADD
  - MCAD
  - LCHAD
  - TFP
  - VLCAD
- Endocrine Disorders
  - CAH
  - CH
- Enzyme disorders:
  - GALT
  - BIOT
- Hemoglobinopathies
  - Hgb SC, BARTS, Sickle B thal.

False positives- parental nutrition, antibiotics

False negatives- rare, enzyme immaturity


Newborn screen
Normal
Abnormal
Symptoms Persist
No symptoms
Confirmatory test
Genetic consult
Negative
Positive
Reassure
Heterozygous
Disease
Counsel
Management
Genetic consult

OVERVIEW OF METABOLIC DISORDERS

- Classification
- Clinical presentation
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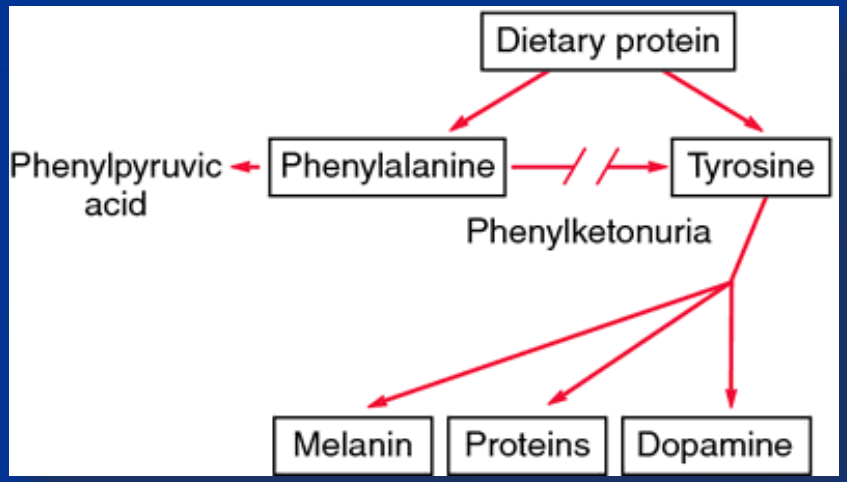
- Principles of treatment

AMINO ACIDOPATHIES

PHENYLKETONURIA (PKU)

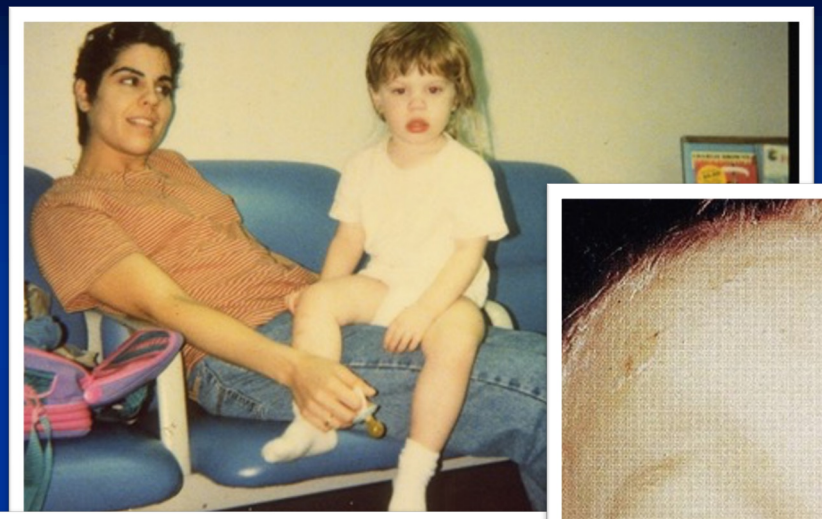
- 1:10000 (Caucasians)
- Deficiency of phenylalanine hydroxylase (PAH)
- Sx:
  - Developmental delay
  - Seizures
  - Eczema
  - Microcephaly
- Dx:
  - Classic PKU - phenylalanine levels >20
  - Hyperphenylalanemia - phenylalanine levels 2-20
- Tx:
  - Low phenylalanine diet (lifelong)
  - Palynziq injections – pegvaliase-pqpz (phe metabolizing enzyme)

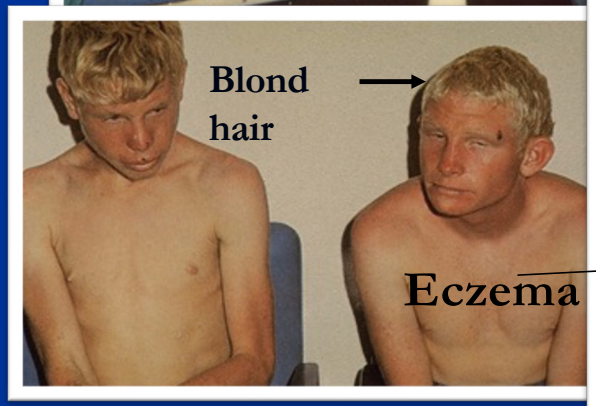


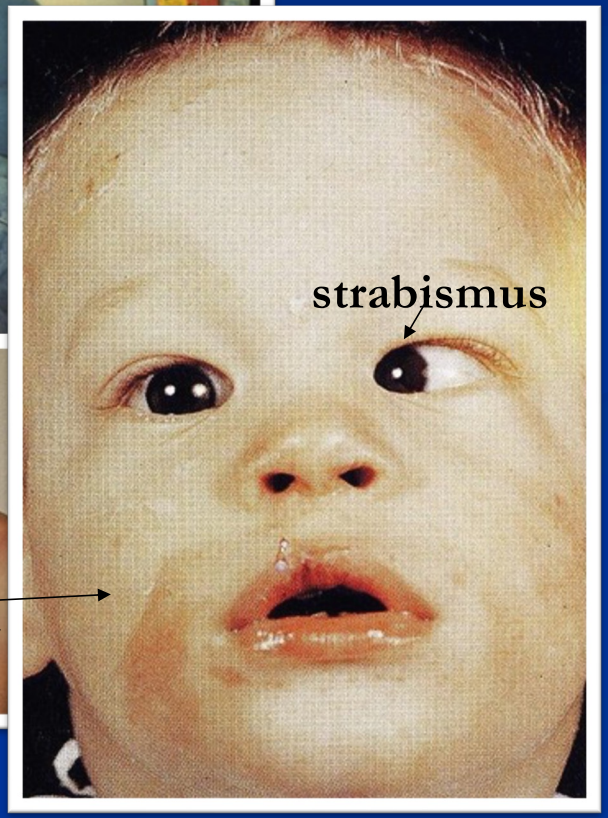
PHENYLKETONURIA: MATERNAL PKU

- Teratogenic effects on the fetus from maternally-elevated phenylalanine (mother not on diet)
  - Microcephaly, cleft lip/palate, congenital heart defects, and IUGR
  - Dietary management/treatment must begin **prior to conception**

UNTREATED PKU



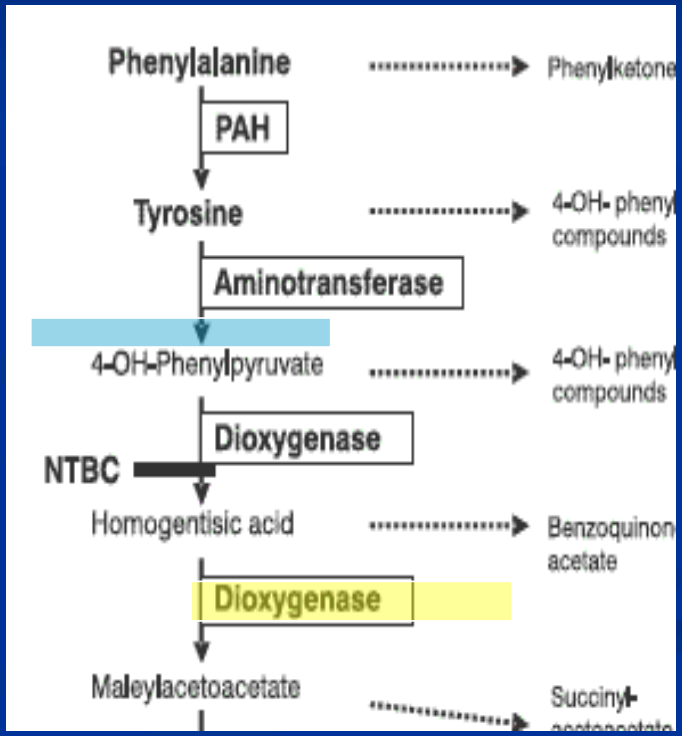




TREATED PKU

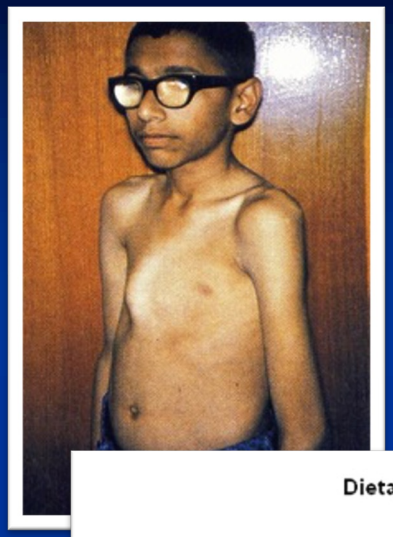
TYROSINEMIA TYPE I

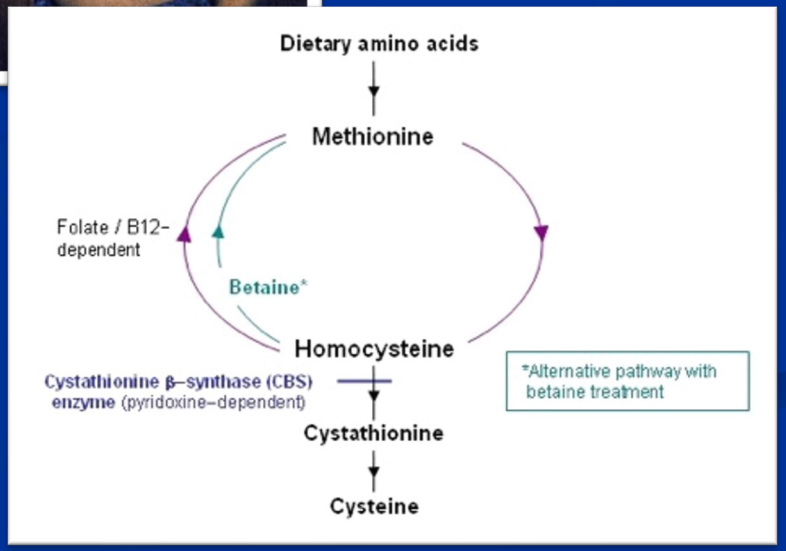
- 1:110000 live births
- Deficiency of fumarylacetoacetase hydrolase (FAH)
- Sx:
  - Liver, Kidney, Skeletal (rickets), Neurologic abnormalities
  - 40% hepatic carcinoma by 5 years
- Dx:
  - PAA - increased Tyrosine
  - NBS: Succinylacetone +
- Tx:
  - NTBC
  - Low phenylalanine
  - Low tyrosine diet



HOMOCYSTINURIA

- 1:300000 live births
- Deficiency of cystathione B synthetase
- Sx:
  - Marfanoid: unusually tall, long limbs/arachnodactyly, pectus, osteoporosis, scoliosis, myopia, dislocated lenses, ID, psych abnormalities, seizures, thromboembolism
- Dx:
  - Plasma amino acids - increased methionine
  - Increased homocysteine
- Tx:
  - B6, B12, folate, betaine, Methionine restriction

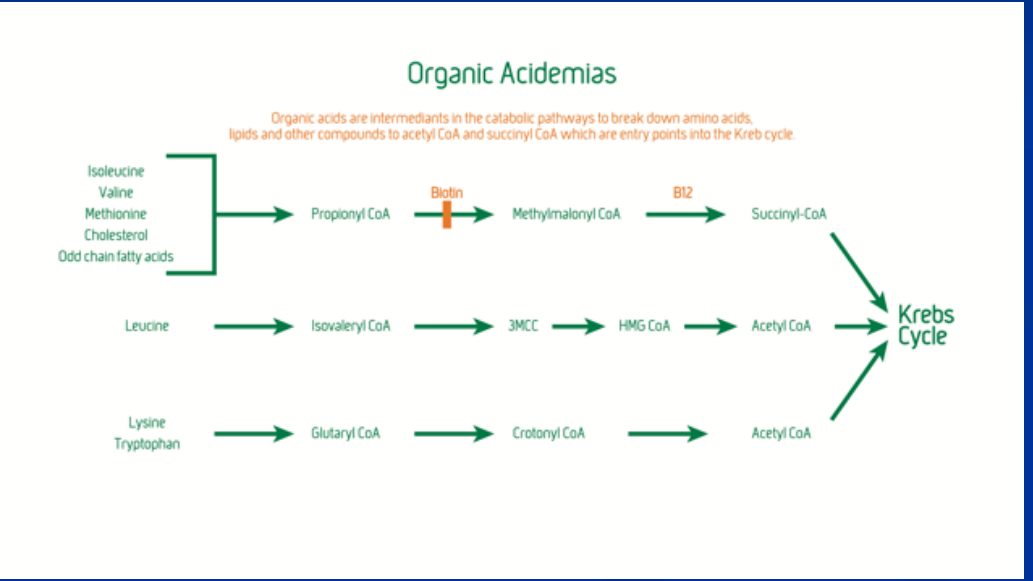




ORGANIC ACIDEMIAS

ORGANIC ACIDEMIAS

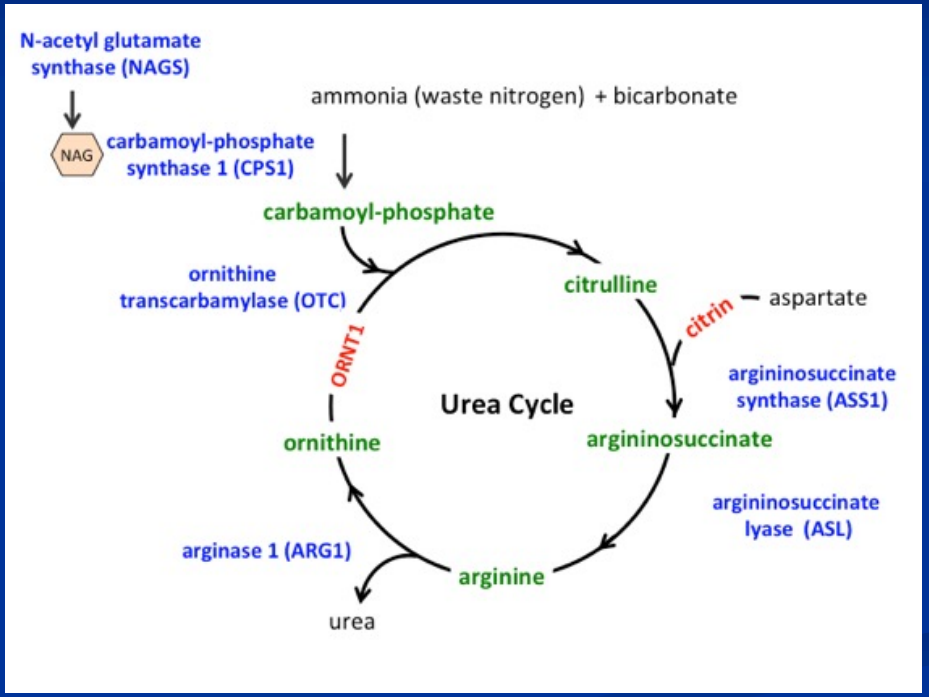
- ~1:100000 live births
- Sx:
  - 1st week: poor feeding, vomiting, lethargy, hypotonia, metabolic acidosis (HIGH AG)
  - Later onset: lethargy, vomiting, FTT, seizures, acute metabolic decompensation associated with intercurrent illness
  - Cerebral OA (GA1) – later onset
  - Hyperammonemia
  - Metabolic acidosis (HIGH anion gap)
  - BM suppression, dehydration
- Dx:
  - Acylcarnitine profile + Urine Organic Acids
- Tx:
  - Stop insult (PROTEIN)
  - Divert metabolism from protein to carb/fat (high glucose, high lipid!)
  - Fix source of catabolism (ex. infection, trauma, surgery)
  - Ammonia scavengers



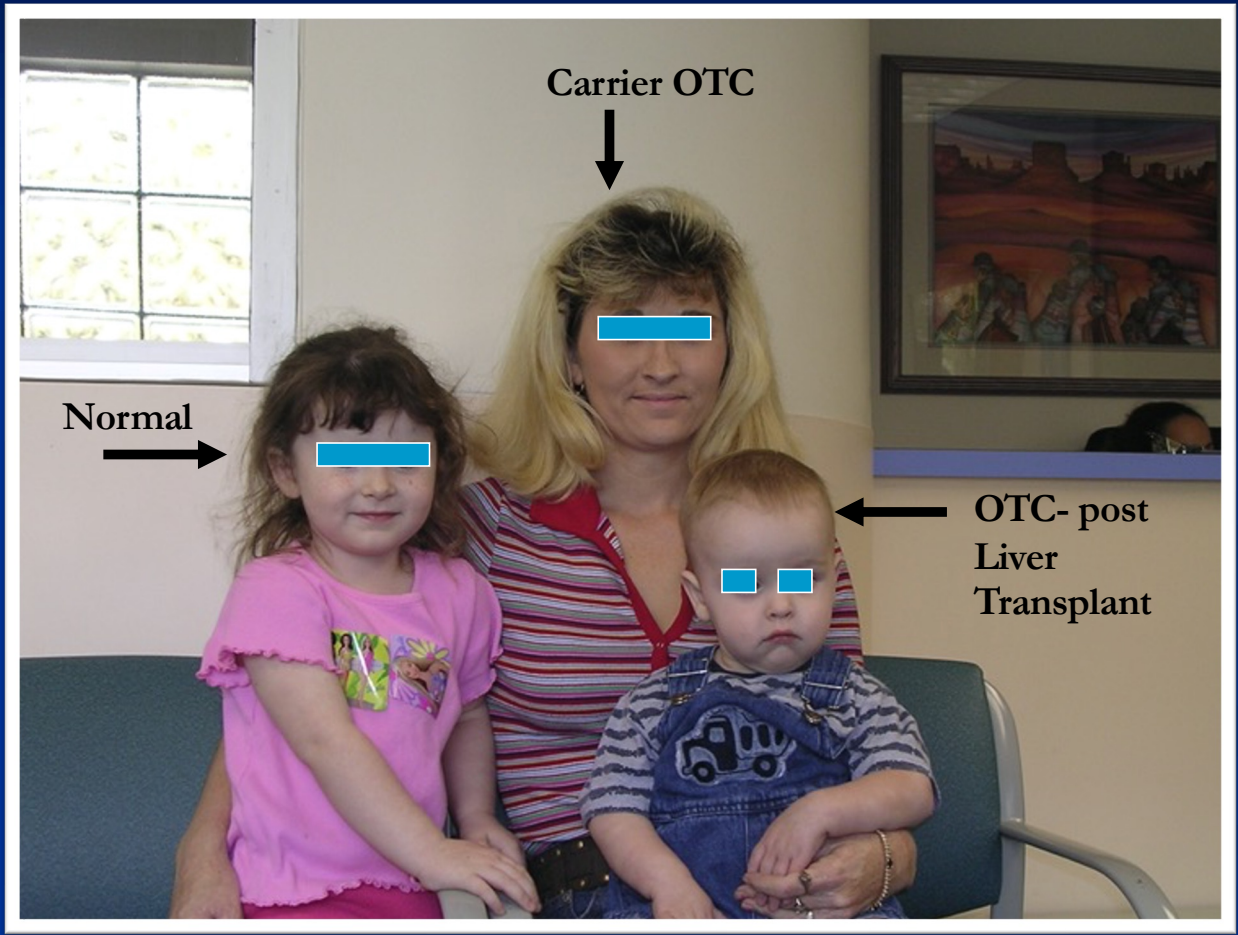
UREA CYCLE DISORDERS

UREA CYCLE DEFECTS

- 1:30000 live births
- Sx:
  - 1st week: poor feeding, tachypnea, vomiting, lethargy (hyperammonemia)
  - Seizures
  - Neonatal coma
- Dx:
  - Hyperammonemia
  - Respiratory alkalosis
  - Absence of ketoacidosis
  - Normal/low BUN
- Tx:
  - Stop insult (PROTEIN)
  - Divert metabolism from protein to carb/fat (high glucose, high lipid!)
  - Ammonia scavengers



OTC – X-LINKED!



CAUSES OF HYPERAMMONEMIA

- Urea cycle defects
- Organic acid abnormalities
- Fatty acid oxidation defects - MCAD/LCHAD
- Mitochondrial - pyruvate dehydrogenase deficiency

FATTY ACID OXIDATION DEFECTS

FATTY ACID OXIDATION DEFECTS

Clinical:

- Hypoglycemia
- Liver dysfunction
- Recurrent vomiting, lethargy, coma
- SIDS/Reyes like episodes
- Cardiomyopathy
- Myoglobinuria
- HELLP Syndrome in mothers and LCHAD in babies

Biochemical:

- Hypoketotic hypoglycemia
- Low carnitine
- Abnormal organic acids, acylcarnitines, acylglycines
- +/- Hyperammonemia

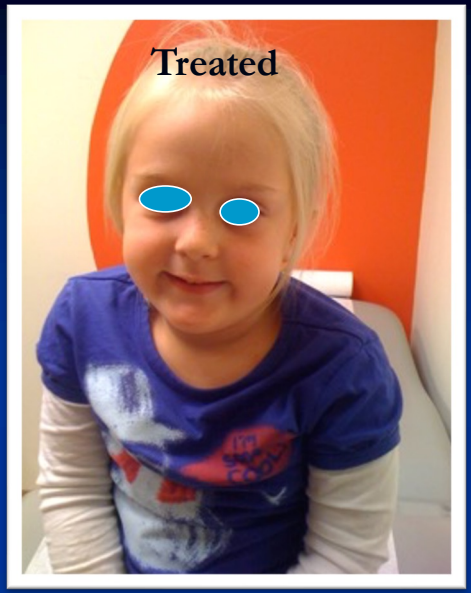
- Treatment:
- Carnitine
- Low fat diet
- Avoid fasting

FATTY ACID OXIDATION DEFECTS

MCAD- NBS diagnosis

VLCAD- Diagnosed at 16 months

BIOTINIDASE DEFICIENCY

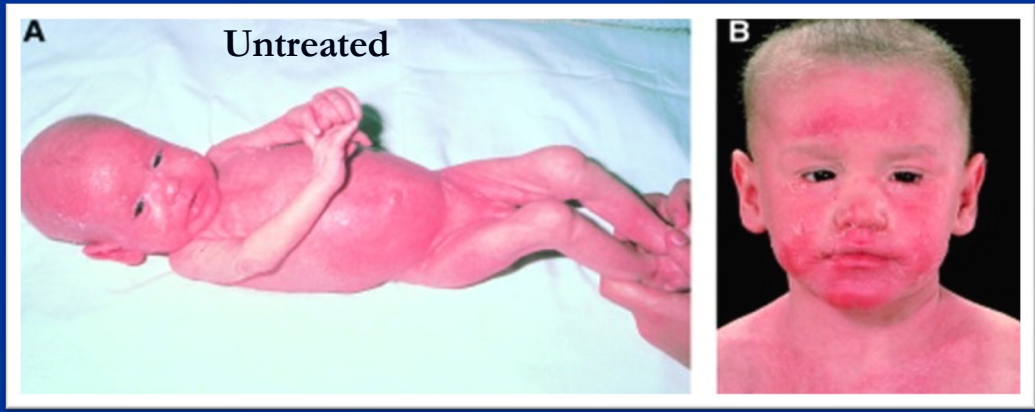


Sx:

- Seizures, hypotonia, ataxia
- Developmental delay
- Vision problems, hearing loss
- Cutaneous abnormalities (e.g., alopecia, skin rash, candidiasis)

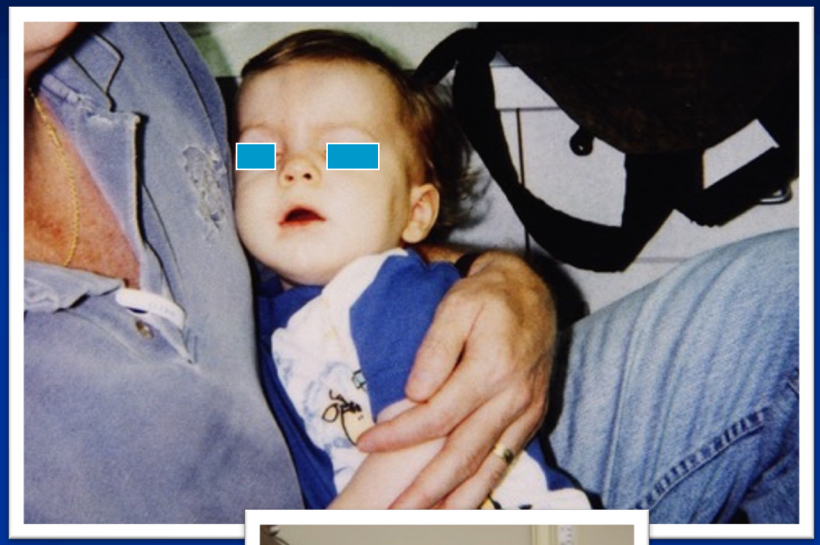
Older children and adolescents:

- Motor limb weakness, spastic paresis, and decreased visual acuity



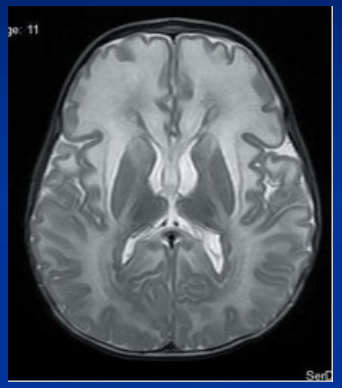
CANAVAN DISEASE

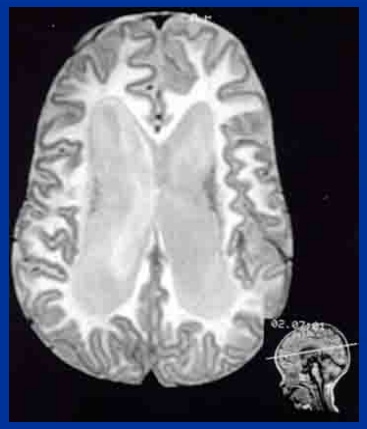
- AR; 1:40 carrier frequency (Ashkenazi Jewish; 3 mutations ~98% of alleles)
- Sx:
  - Progressive leukodystrophy, macrocephaly, ID, seizures, optic atrophy
- Dx:
  - Increased urinary NAA
- Tx:
  - Symptomatic



CAUSES OF MACROCEPHALY

- Alexanders disease
- L-2 hydroxyglutaric aciduria
- Canavan
- Glutaric aciduria- 1





Canavan- demyelination with diffuse white matter changes

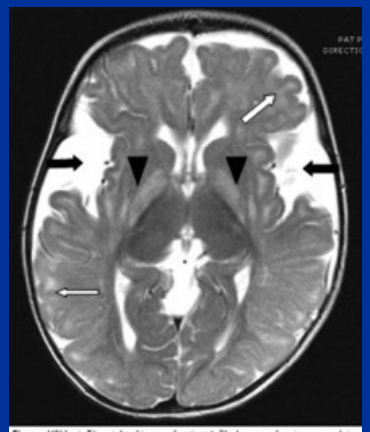
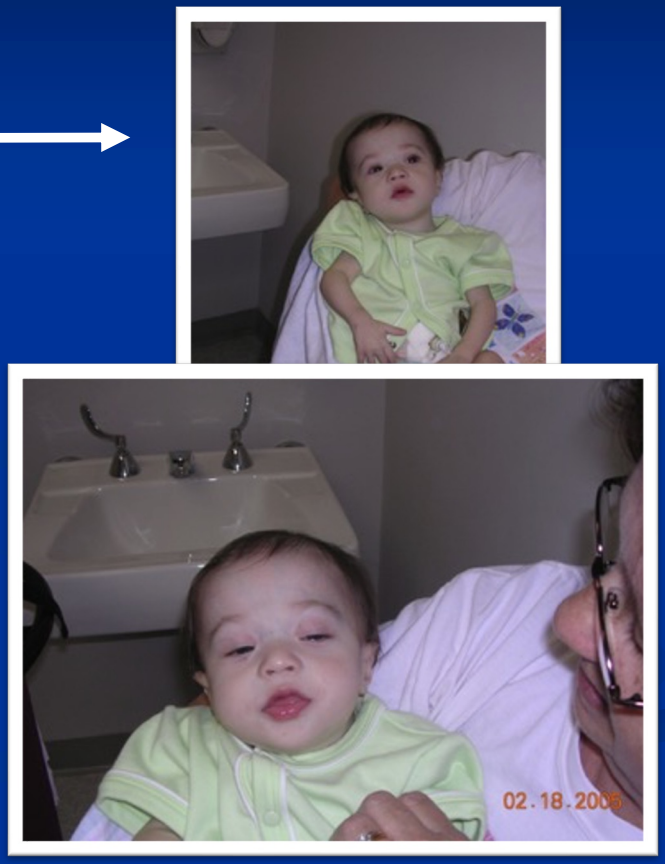


Figure: MRI brain T2-weighted image of patient 1. Black arrows showing open sylvian fissure secondary to fronto-temporal atrophy, black arrow heads showing hyperintense signals in globes pallidus, white arrows showing delayed myelination.

PEROXISOMAL DISORDERS

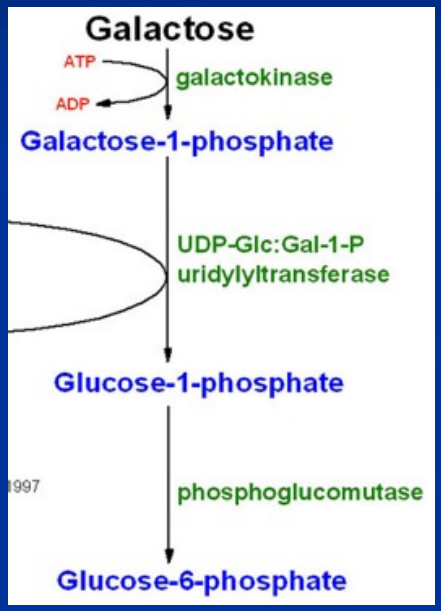
- Zellweger (Increased VLCFA)
- Neonatal Adrenoleukodystrophy (increased VLCFA)
- Refsum (Increased phytanic acid)

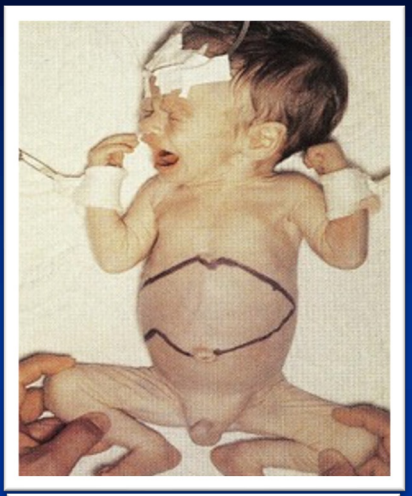


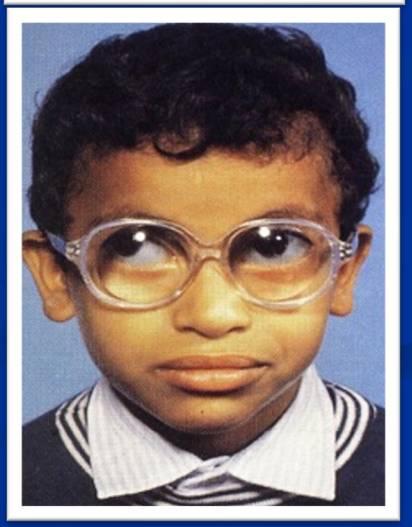
CARBOHYDRATE METABOLISM

GALACTOSEMIA

- Autosomal recessive
- Gal-1-P-uridyl transferase (GALT) deficiency
- Sx:
  - Vomiting, diarrhea, liver disease, cataracts, E coli sepsis, infertility, speech delay
  - Hyperchloremic metabolic acidosis
- Dx: Gal-1-P RBC, galactosuria
- Tx:
  - Lactose-free diet





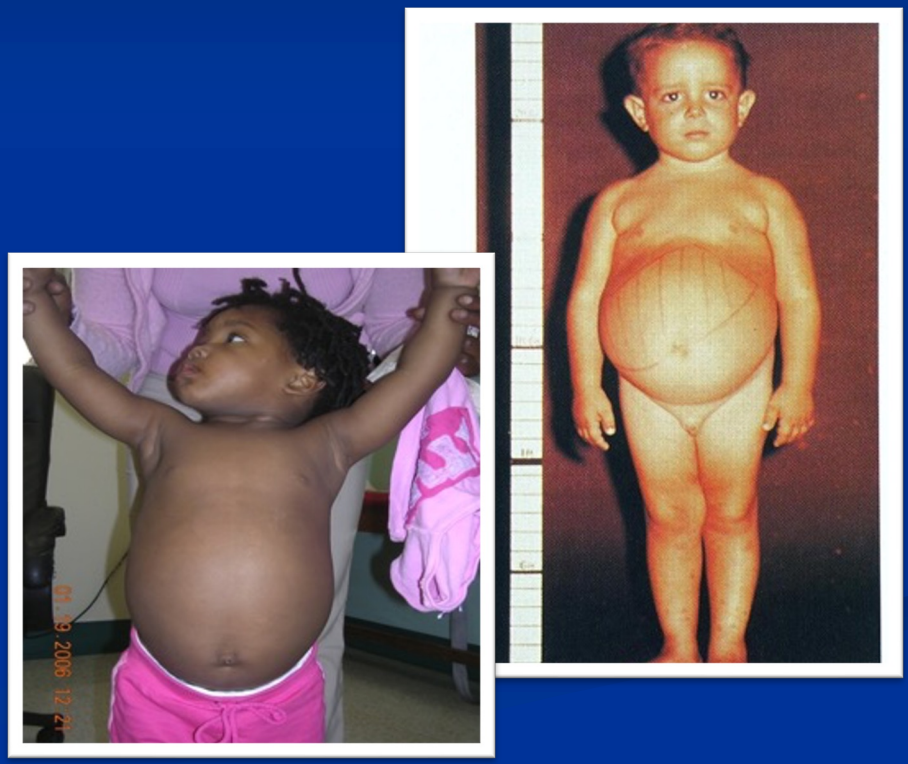


CAUSES OF CATARACTS

- Galactosemia
- Homocystinuria
- Fabry disease
- Lowe syndrome
- Zellweger syndrome

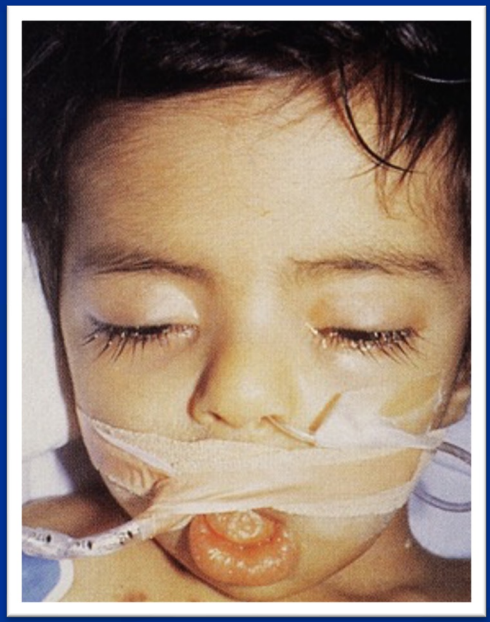
GLYCOGEN STORAGE DISEASE TYPE I (VON GIERKE)

- Hepatic glucose-6-phosphatase deficiency
- Sx:
  - Hypoglycemia in early infancy
  - Protuberant abdomen due to (hepatomegaly)
  - Doll's facies or cherubic face
- Dx:
  - Liver biopsy for enzyme activity
  - DNA analysis
- Tx:
  - Frequent feeds
  - Raw cornstarch (older kids)
  - Nocturnal glucose infusions



GLYCOGEN STORAGE DISEASE TYPE 2 (POMPE)

- Acid maltase deficiency
- Sx:
  - Cardiomegaly, increased CPK, macroglossia
    Hypotonia
- EKG:
  - Short PR interval, large QRS complex
- Tx:
  - Enzyme replacement- Myozyme

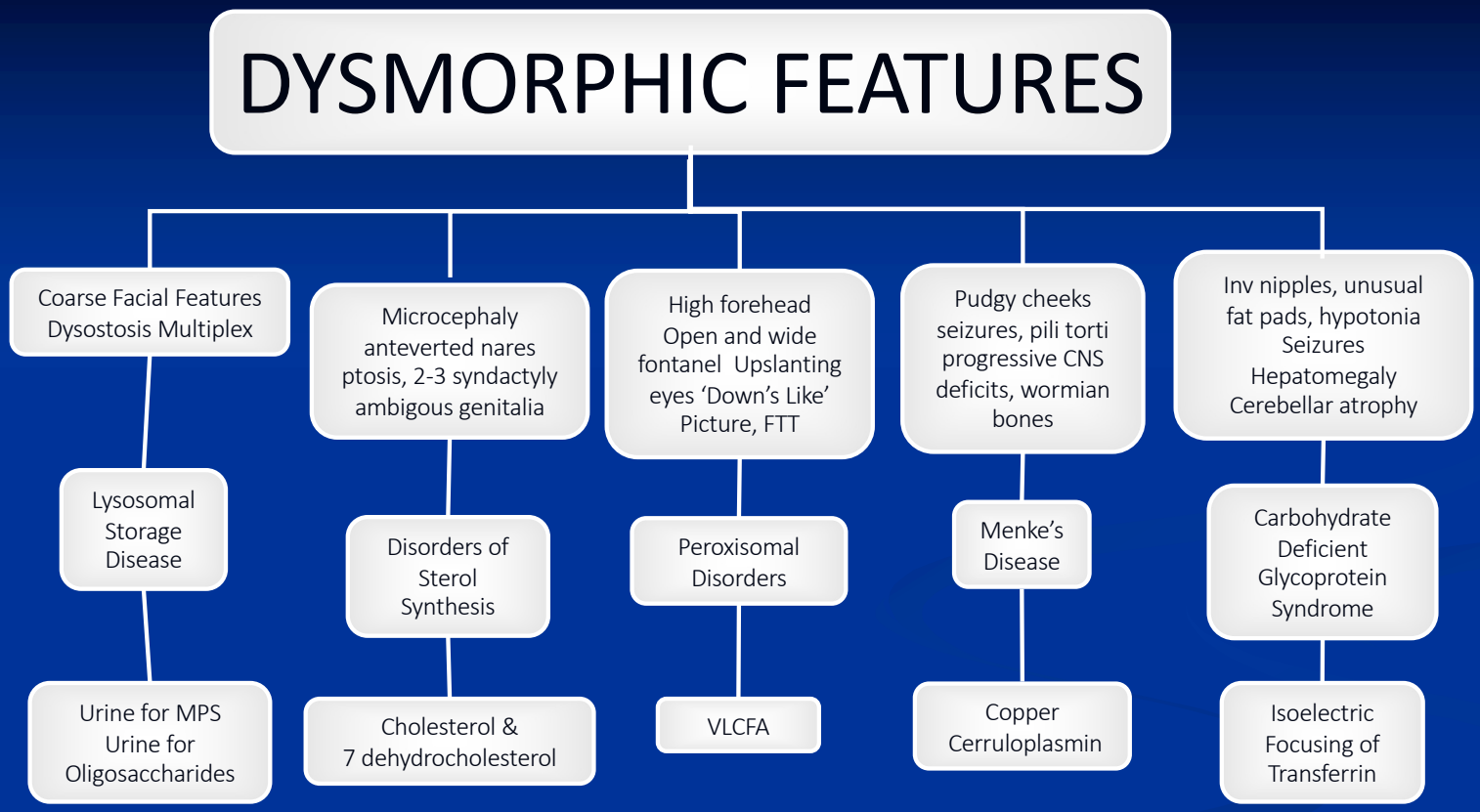


CAUSES OF CARDIOMYOPATHY

- Pompe
- Glycogen storage type 3
- Fatty acid oxidation defects
- Mucopolysaccharidosis

LYSOSOMAL STORAGE DISORDERS

DYSMORPHIC FEATURES



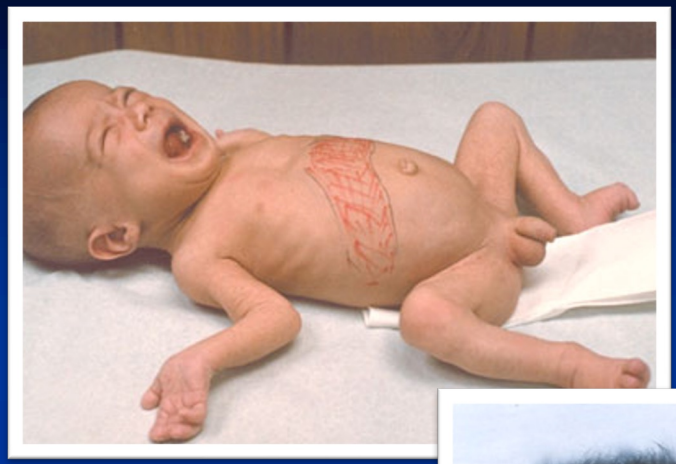
- MPS – Mucopolysaccharidosis
- VLCFA – Very Long Chain Fatty Acids

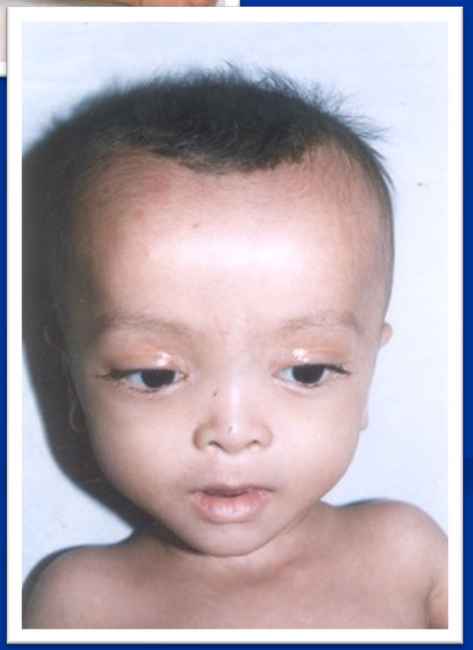
DYSMORPHIC FEATURES

HIGH FOREHEAD
OPEN AND WIDE FONTANEL
UPSLANTING PALPEBRAL FISSURES
FTT, SEIZURES
GLAUCOMA, RETINAL DEGENERATION
IMPAIRED HEARING

PEROXISOMAL DISORDERS
ZELLWEGER SYNDROME

INCREASED VLCFA





DYSMORPHIC FEATURES

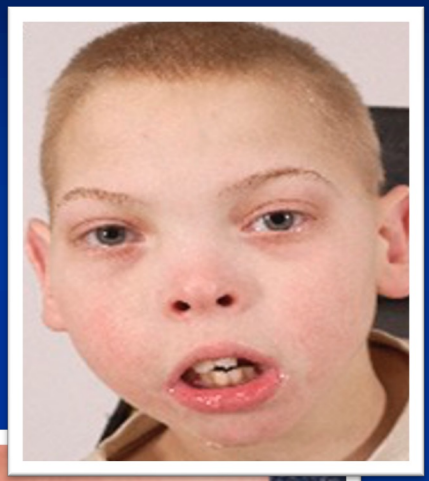
Microcephaly
anteverted nares
ptosis, 2-3
syndactyly ambigous
genitalia

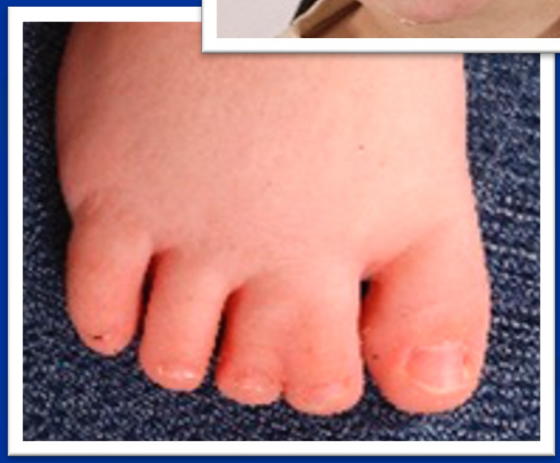
↓

Disorders of
Sterol
Synthesis

↓

Cholesterol &
7-dehydrocholesterol





DYSMORPHIC FEATURES

INV NIPPLES, UNUSUAL
FAT PADS, HYPOTONIA SEIZURES
HEPATOMEGALY
CEREBELLAR ATROPHY

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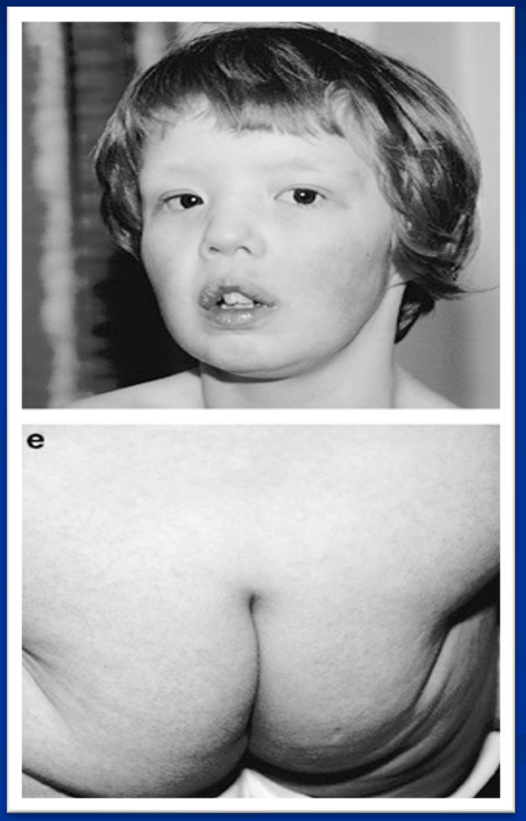
CARBOHYDRATE DEFICIENT
GLYCOPROTEIN SYNDROME

↓

ISOELECTRIC FOCUSING OF
TRANSFERRIN

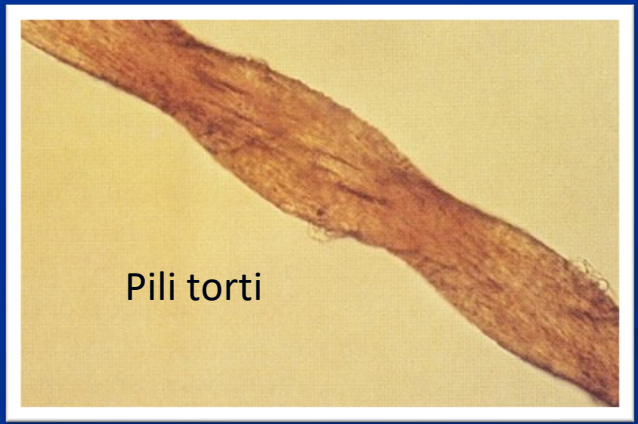


DYSMORPHIC FEATURES

PUDGY CHEEKS SEIZURES, PILI TORTI PROGRESSIVE CNS DEFICITS, HYPOTONIA, WORMIAN BONES, SUBDURAL HEMATOMA

MENKE'S DISEASE
X-LINKED RECESSIVE

LOW COPPER
LOW CERRULOPLASMIN

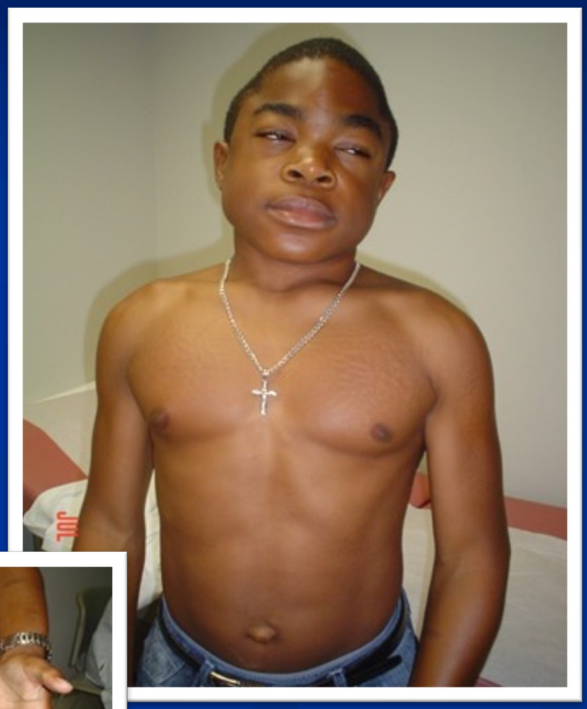


DYSMORPHIC FEATURES

COARSE FACIAL FEATURES
DYSOSTOSIS MULTIPLEX

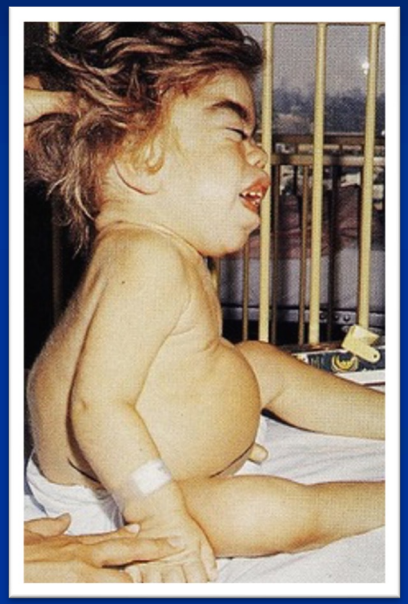
LYSOSOMAL
STORAGE
DISEASE

URINE FOR MPS
URINE FOR
OLIGOSACCHARIDES

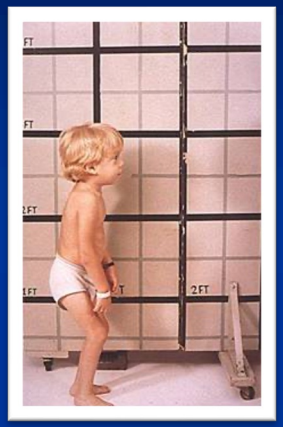


HURLER SYNDROME (MPS I)

- Autosomal recessive
- Iduronidase deficiency
- Sx:
  - Corneal clouding
  - Intellectual disability
  - Coarse Facies
  - Dysostosis multiplex
- Dx:
  - Dermatan sulfate + Heparin sulfate - urine
- Tx:
  - ERT

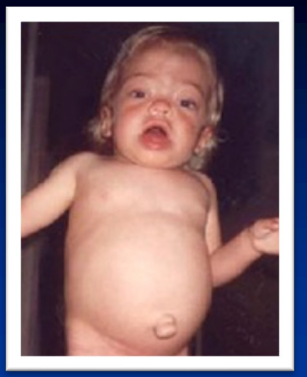


Skeletal deformities (Gibbus)[1]

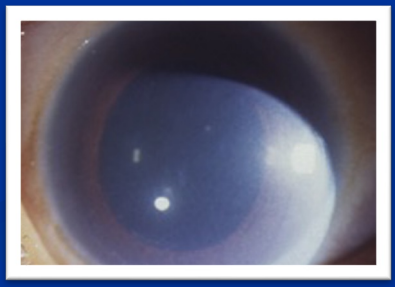


Short stature[2]

Umbilical/inguinal hernia[3]



Hepatosplenomegaly[2]

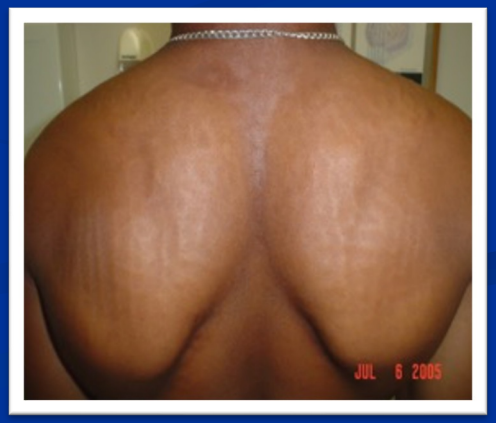


Corneal clouding[3]

Carpal tunnel syndrome[2]

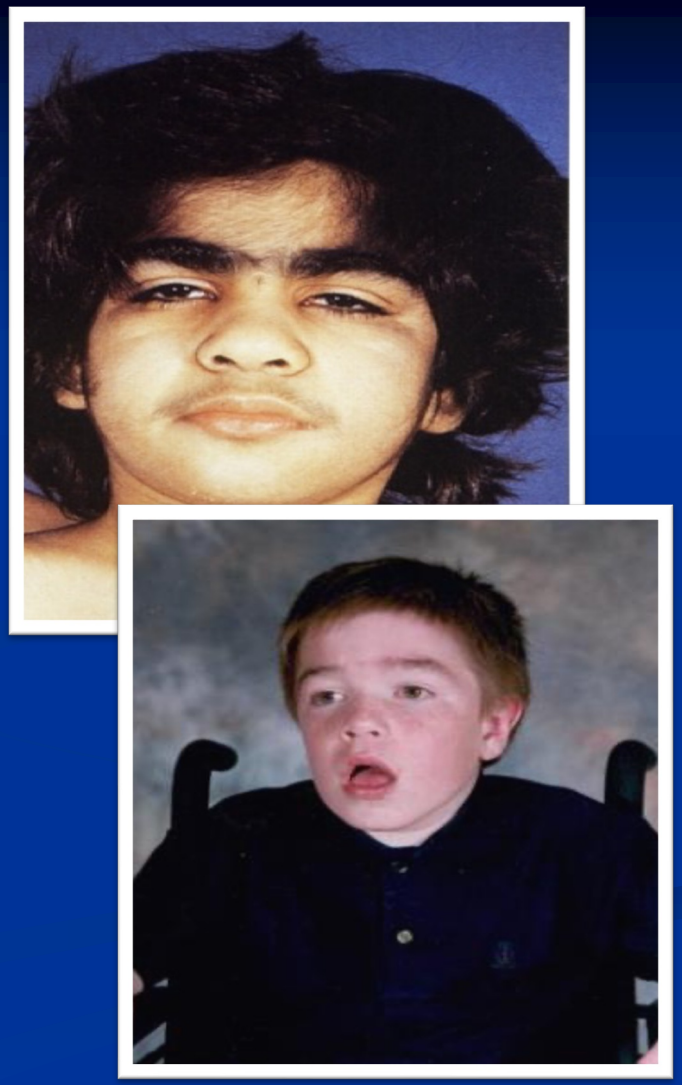
HUNTER SYNDROME (MPS II)

- X-linked recessive
- Iduronate sulphatase deficiency
- Sx:
  - NO corneal clouding
  - Intellectual disability
  - Coarse Facies
  - Dysostosis multiplex
- Dx:
  - Dermatan sulfate + Heparin sulfate - urine
- Tx:
  - Elaprase (ERT)



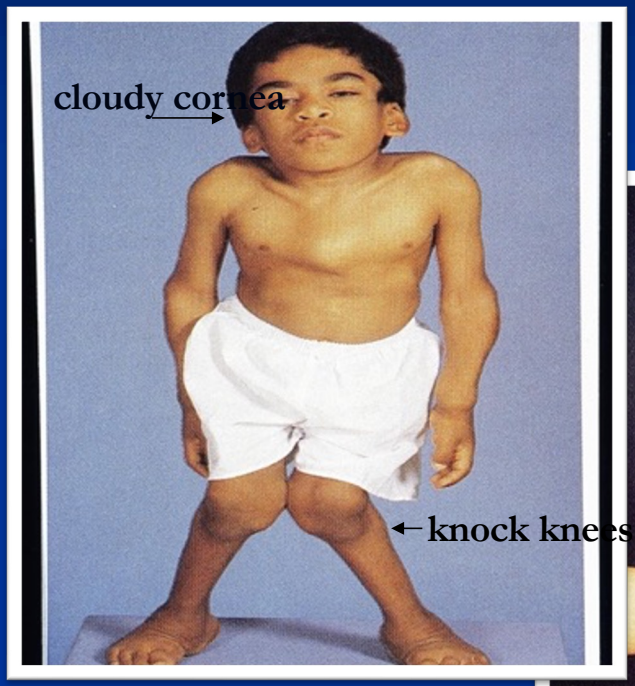
SANFILIPPO (MPS III)

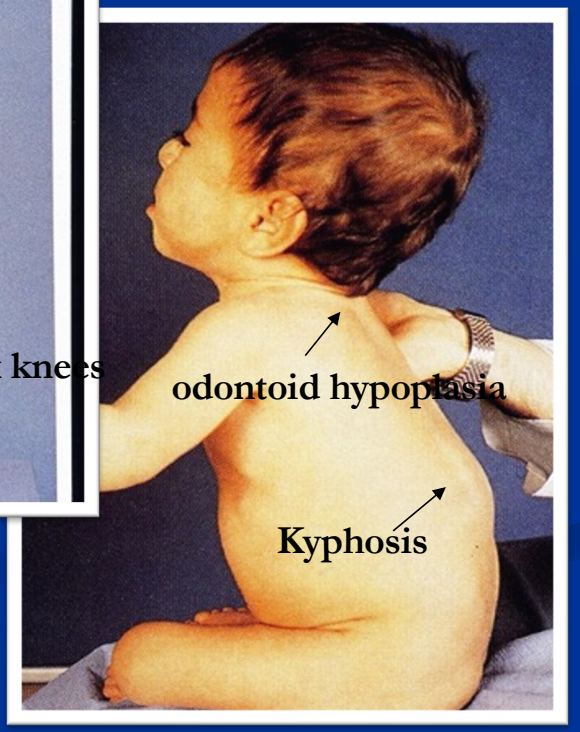
- Autosomal recessive
- Many “flavors” (IIIA, IIIB, IIIC, IIID)
- Sx:
  - Intellectual disability
  - ADHD
  - Sleep disturbance
  - Severe behavior problems
  - Mild skeletal changes
- Dx:
  - Heparan sulfate – urine
- Tx:
  - ERT
  - Gene therapy



MORQUIO SYNDROME (MPS IV)

- Autosomal recessive
- Many “flavors” (A, B, C)
- Sx:
  - Short trunk dwarfism
  - Valvular heart disease
  - Odontoid hypoplasia
  - Normal intelligence
- Dx:
  - Keratin sulfate - urine
- Tx:
  - ERT



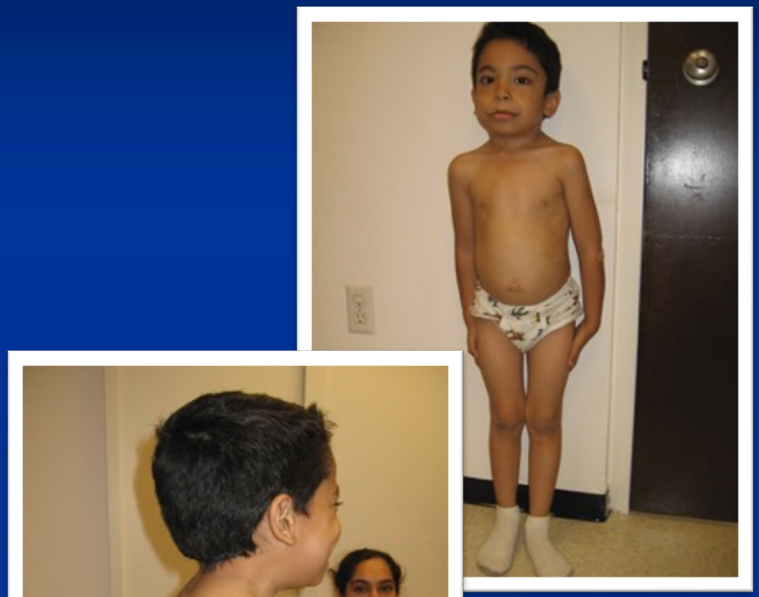


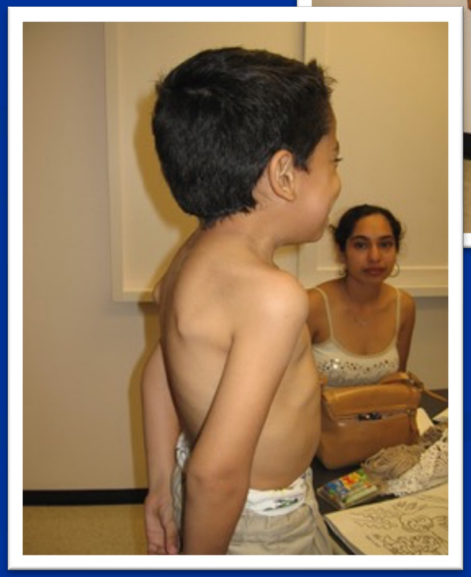
MAROTEAUX-LAMY SYNDROME (MPS VI)

- Arylsulphatase B deficiency
- Sx:
  - Growth arrest - 1-3 years
  - Corneal clouding
  - Coarse facies
  - Joint stiffness
  - Dysostosis multiplex
  - Valvular heart disease
  - NORMAL intelligence
- Dx:
  - Dermatan sulfate - urine
- Tx:
  - ERT

SLY SYNDROME - MPS VII

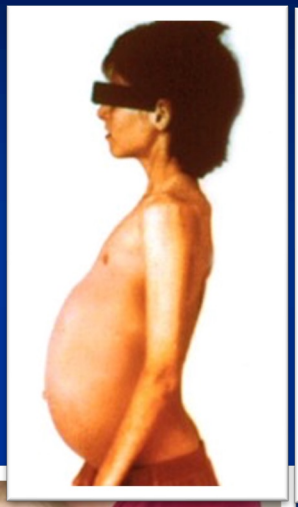
- B-glucuronidase deficiency
- Sx:
  - Prenatal onset hydrops/ascites
  - Severe intellectual disability
  - Corneal clouding
  - Hepatosplenomegaly
  - Skeletal changes

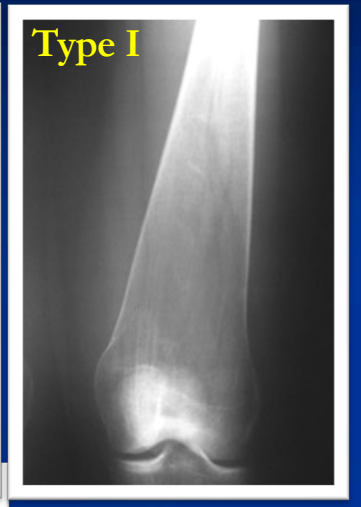


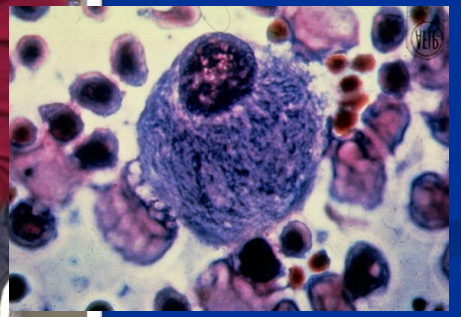


GAUCHER DISEASE

- Autosomal recessive
- 1:500-1000 (Ashkenazi Jewish)
- B-glucocerebrosidase deficiency
- Sx:
  - Type I – Non-neuronopathic (NO CNS INVOLVEMENT)
    - (AJ carrier frequency 1:14)
    - HSM, anemia/bleeding tendencies, abdominal pain, skeletal deformities, bone pain
    - Tx: ERT (Cerezyme) – does not cross BBB!
  - Type II- Neuronopathic (Severe CNS)
    - HSM, ophthalmoplegia, spasticity -- progressive
    - No ethnic predominance
    - Fatal by 2 years of age
  - Type III – "Mild" neuronopathic
    - HSM, Horizontal supranuclear gaze palsy (IIIB), Cardiac calcifications (IIIC)
- Dx:
  - Foam cells - histology





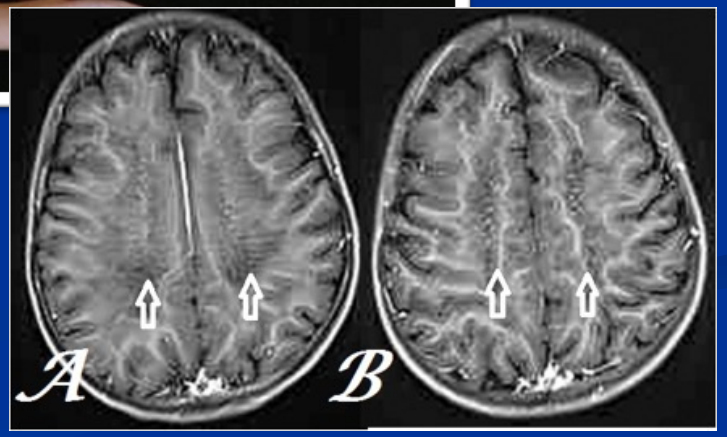


Bone Marrow Macrophage
Engorged with Glucosylceramide

LEUKODYSTROPHIES

METACHROMATIC:

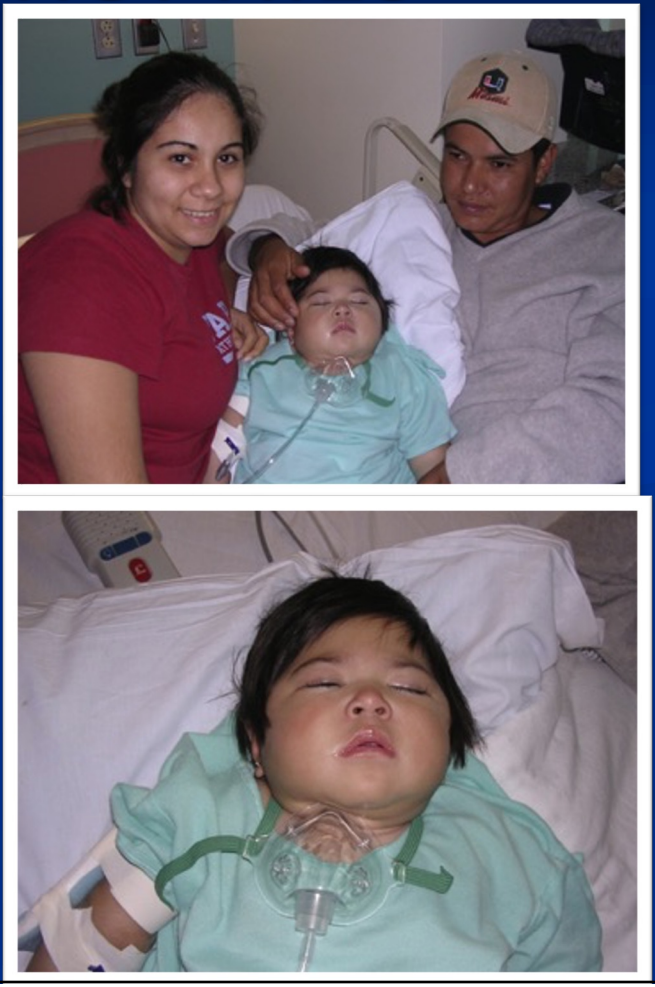
- Autosomal recessive
- Arylsulfatase A deficiency
- Sx:
  - Developmental delay, ataxia, optic atrophy
  - Neuroregression
- Dx:
  - Decreased ARSA – leukocytes
  - Increased sulfatides - urine
- Tx:
  - Symptomatic



LEUKODYSTROPHIES

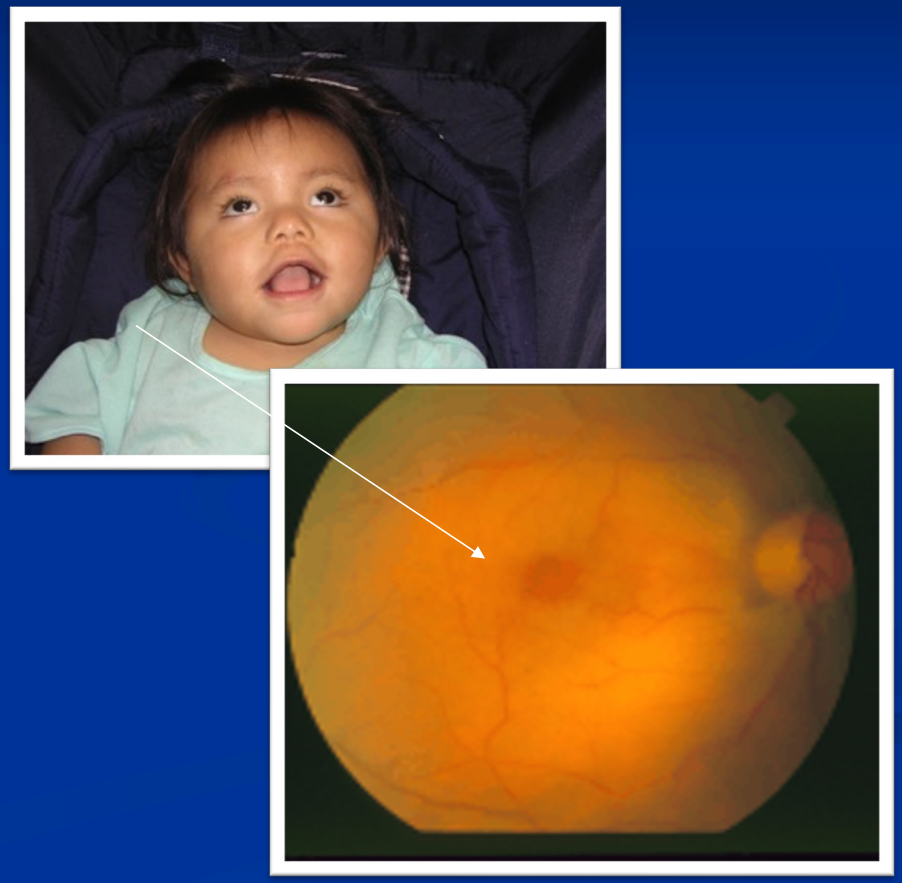
KRABBE:

- Galactocerebrosidase deficiency
- Sx:
  - Onset <6 mo
  - Hypertonia, irritability
  - Deafness, blindness (optic atrophy)
  - Exaggerated startle reflex
  - Increased CSF protein, abnormal MRI
- Tx:
  - Symptomatic



TAY SACHS DISEASE

- Hexosamidase A Deficiency
  - Inability to degrade GM2 ganglioside
- Sx:
  - 6-12 months: slowing development, hyperacusis, apathy, cherry red macula, seizures, blindness, spasticity (exaggerated startle reflex)
  - Death by 2-5 years
- Late onset with residual activity
  - Motor neuron dysfunction, ataxia but normal IQ and vision (although 1/3 have psychosis)



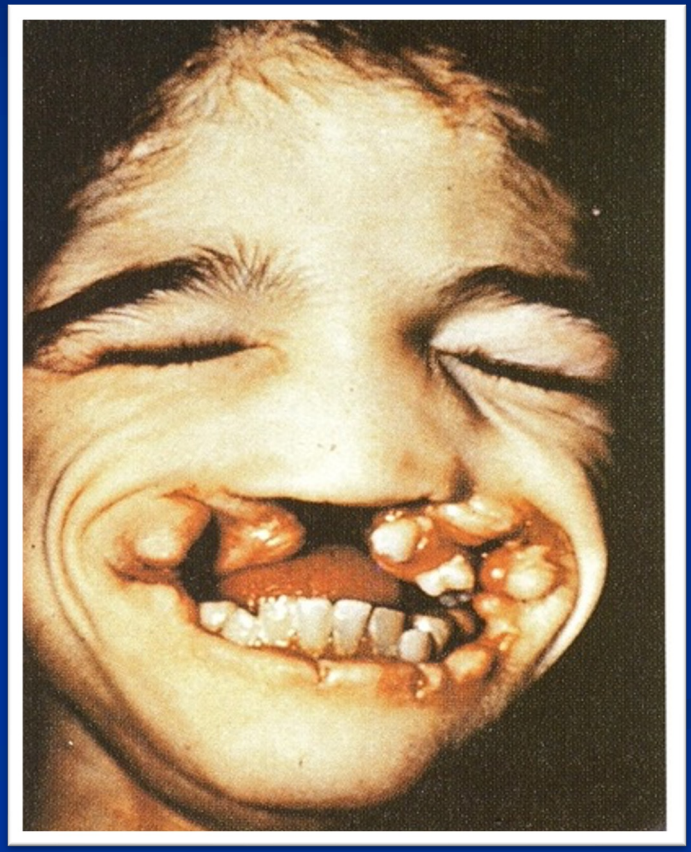
CAUSES OF CHERRY RED MACULA

- Tay Sachs disease
- Sandhoff
- GM 1 Gangliosidosis
- Niemann-Pick disease
- Sialidosis
- Mucolipidosis

PURINE/PYRIMIDINE

LESCH-NYHAN:

- X-linked recessive
- HGPRT deficiency
- Sx:
  - Normal at birth
  - Intellectual disability
  - Choreiform movements
  - Self mutilation, gout
- Dx:
  - Increased uric acid
  - MRI: basal ganglia abnormalities
- Tx:
  - Allopurinol
  - Symptomatic



Metabolic Disorders

- Classification
- Clinical presentation
- Newborn screen
- Common metabolic disorders
- **Principles of treatment**

ACUTE PHASE MANAGEMENT

Prompt and vigorous treatment of acidosis or hyperammonemia can lead to complete recovery and prove to be life saving

- Arrange transfer to level three facility

ACUTE PHASE MANAGEMENT

- IV benzoate and sodium phenylacetate or phenylbutyrate
  - Excretion of ammonia and waste nitrogen
- Eliminate dietary intake of potentially toxic foods such as protein, galactose, or fructose
- IV glucose
  - Positive caloric balance
  - Promote diuresis
- Vitamins
  - Biotin, vitamin B6, cobalamin, thiamine, or riboflavin
- Hemodialysis for life-threatening metabolic disturbances

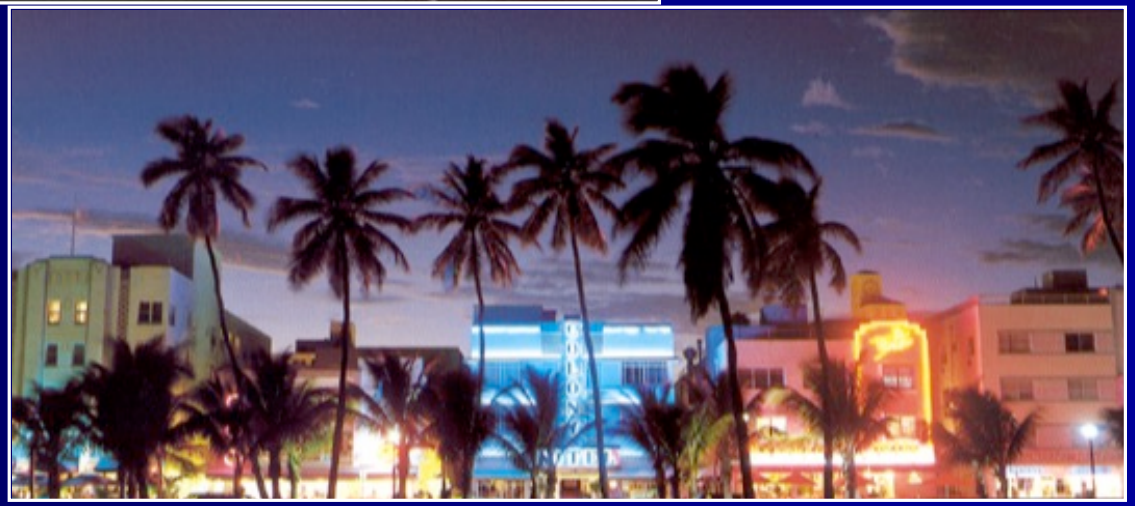
LONG TERM MANAGEMENT

- Augment the activity of an enzyme
  - Ex. Vitamin B12 supplementation in methylmalonic acidemia
- Restrict dietary intake of protein or substrate
  - Dietary treatment of PKU and galactosemia
- Increase excretion of toxic substrate
  - Glycine in isovaleric acidemia
- Enzyme replacement
  - Gaucher, Hurler, Pompe, MPS IV, Hunter
- Organ transplant
  - Liver transplant in hereditary tyrosinemia and OTC

CONCLUSION

- Greater awareness:
  - Greater chance of successful treatment if diagnosed early → reduction in morbidity and mortality
  - The three common conditions we see are urea cycle, fatty acid oxidation and amino acid abnormalities
- Greater index of suspicion:
  - Symptoms that are complex, persistent and/or unexplained by sepsis warrant prompt referral

Thank You



Gracias