26th Annual General Pediatric Review & Self-Assessment

Nicklaus Children's Hospital

METABOLISM

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OBJECTIVES

- DEFINE INBORN ERRORS OF METABOLISM (IEM)
- RECOGNIZE THE IMPORTANCE OF EARLY DIAGNOSIS OF IEM
- CHARACTERIZE COMMON METABOLIC DISORDERS
- DETERMINE PRINCIPLES OF TREATMENT FOR IEM

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OVERVIEW OF METABOLIC DISORDERS

- CLASSIFICATIONS
- CLINICAL PRESENTATION
- NEWBORN SCREEN
- COMMON METABOLIC DISORDERS
- PRINCIPLES OF TREATMENT

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DEFINITION

- INBORN ERRORS OF METABOLISM
  - GROUP OF GENETIC DISORDERS AFFECTING THE FUNCTION OF ENZYMES, TRANSPORTERS, OR OTHER PROTEINS RESPONSIBLE FOR NORMAL METABOLIC PROCESSES
  - SPECIFIC SUBSTANCES IN THE BODY MAY NOT BE PROPERLY SYNTHESIZED, BROKEN DOWN, OR TRANSPORTED → ACCUMULATION OF TOXIC SUBSTANCES AND/OR DEFICIENCIES IN ESSENTIAL MOLECULES

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CLASSIFICATIONS

- AMINO ACID DISORDERS: DEFECTS IN THE METABOLISM OF AMINO ACIDS, THE BUILDING BLOCKS OF PROTEINS
  - EX: PHENYLKETONURIA (PKU), MAPLE SYRUP URINE DISEASE (MSUD), AND HOMOCYSTINURIA
  - PREVALENCE OF 1 IN 1,000 TO 1 IN 2,500 BIRTHS
- ORGANIC ACIDEMIAS: DEFECTS IN THE METABOLISM OF ORGANIC ACIDS
  - EX: PROPIONIC ACIDEMIA, METHYLMALONIC ACIDEMIA, AND ISOVALERIC ACIDEMIA
  - PREVALENCE OF 1 IN 50,000 TO 1 IN 100,000 BIRTHS
- FATTY ACID OXIDATION DISORDERS: DEFECTS IN THE METABOLISM OF FATTY ACIDS FOR ENERGY PRODUCTION
  - EX: MEDIUM-CHAIN ACYL-COA DEHYDROGENASE (MCAD) DEFICIENCY, VERY-LONG-CHAIN ACYL-COA DEHYDROGENASE (VLCAD) DEFICIENCY
  - PREVALENCE OF 1 IN 10,000 TO 1 IN 20,000 BIRTHS

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CLASSIFICATIONS

- LYSOSOMAL STORAGE DISORDERS: DEFECTS IN LYSOSOMAL ENZYMES RESPONSIBLE FOR BREAKING DOWN COMPLEX MOLECULES
  - EX: GAUCHER DISEASE, POMPE DISEASE, AND MUCOPOLYSACCHARIDOSES
  - PREVALENCE OF 1 IN 5,000 TO 1 IN 7,000 BIRTHS
- MITOCHONDRIAL DISORDERS: IMPAIRED MITOCHONDRIAL FUNCTION, WHICH AFFECTS CELLULAR ENERGY PRODUCTION
  - AFFECT VARIOUS ORGANS AND SYSTEMS IN THE BODY
  - EXACT PREVALENCE AND INCIDENCE RATES UNKNOWN
- UREA CYCLE DISORDERS: DEFECTS IN THE UREA CYCLE, WHICH IS RESPONSIBLE FOR REMOVING TOXIC AMMONIA FROM THE BODY
  - EX: ORNITHINE TRANSCARBAMYLASE (OTC) DEFICIENCY AND ARGININOSUCCINIC ACIDURIA
  - PREVALENCE OF 1 IN 8,000 TO 1 IN 44,000 BIRTHS

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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

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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,

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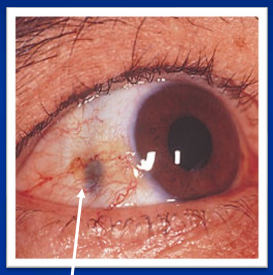
URINE COLOR

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



Ochronosis

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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

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LABORATORY SCREENING TESTS

- LACTATE
- AMMONIA
- PLASMA AMINO ACIDS
- URINARY ORGANIC ACIDS /URINE ACYLGLYCINES
- ACYLCARNITINE PROFILE
- CARNITINE
- BIOTINIDASE

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EXPANDED NEWBORN SCREENING

- PRESYMPTOMATIC DETECTION
- REDUCE MORBIDITY/MORTALITY

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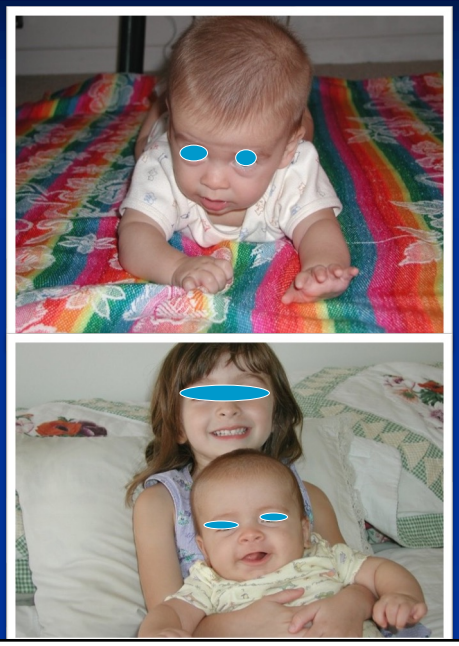
NORMAL DEVELOPMENT
AT 5 MONTHS



NEUROREGRESSION
DX'ED WITH GLUTARIC ACIDURIA 1

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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
  - GA1
  - 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

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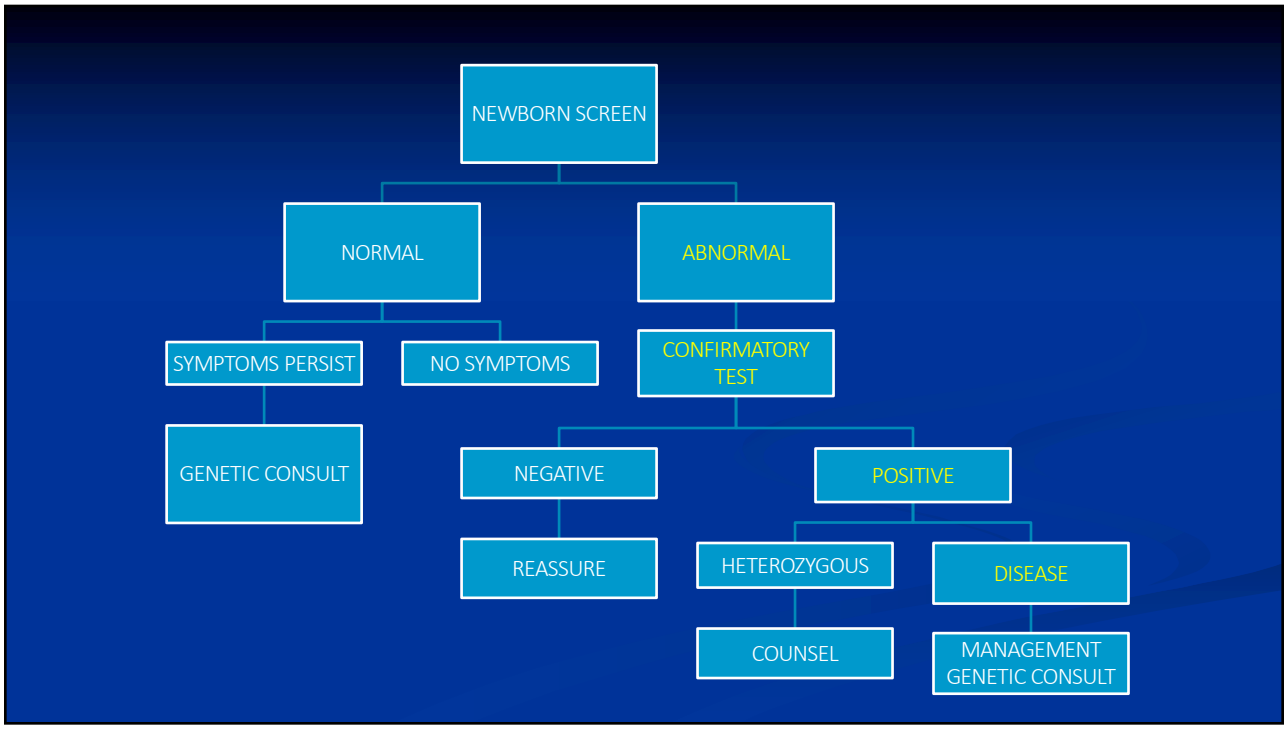

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AMINO ACID METABOLISM

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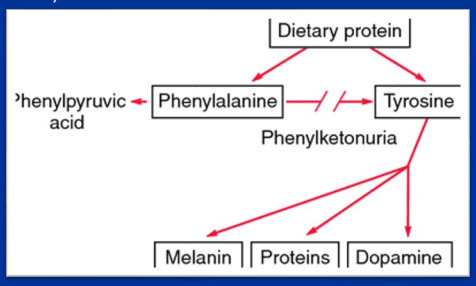
PHENYLKETONURIA (PKU)

- 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)



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PHENYLKETONURIA: MATERNAL PKU

- TERATOGENIC EFFECTS ON THE FETUS FROM MATERNALLY-ELEVATED PHENYLALANINE (MOTHER NOT ON DIET)
  - MICROCEPHALY, CLEFT LIP/PALATE, CONGENITAL HEART DEFECTS, IUGR
  - DIETARY MANAGEMENT/TREATMENT MUST BEGIN PRIOR TO CONCEPTION

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UNTREATED PKU

TREATED PKU

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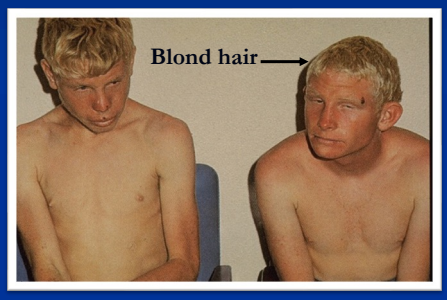
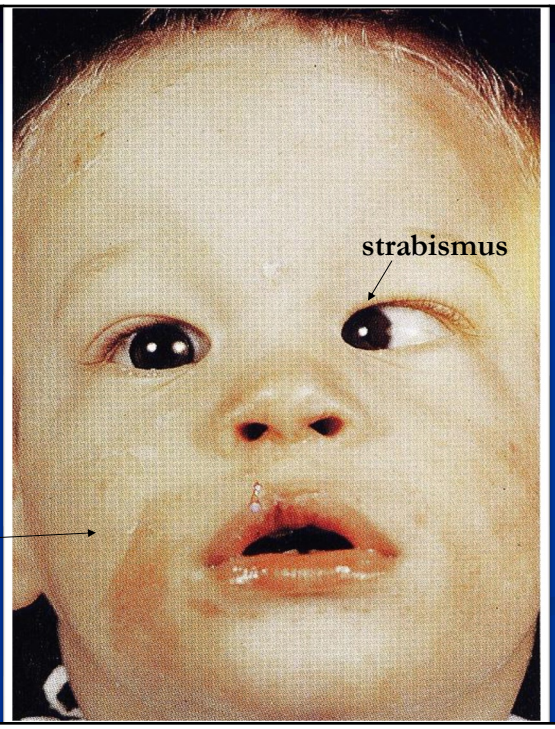
PKU: UNTREATED





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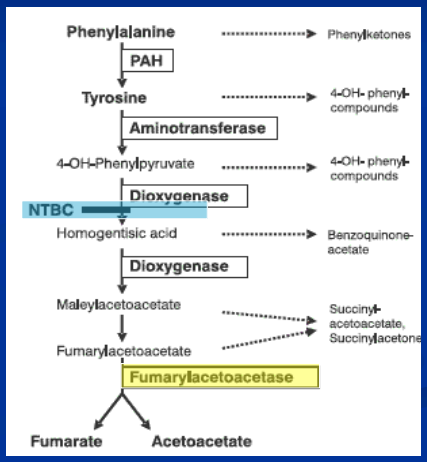
TYROSINEMIA TYPE I

- 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



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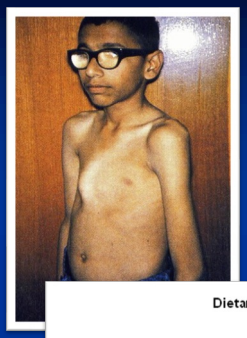
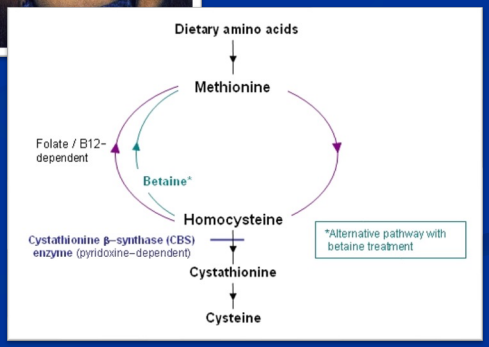
HOMOCYSTINURIA

- INCIDENCE: 1/300000
- DEFICIENCY OF CYSTATHIONE B SYNTHETASE
- SX:
  - MARFANOID: UNUSUALLY TALL, LONG LIMBS/ARACHNODACTYLY, PECTUS, OSTEOPOROSIS, SCOLIOSIS, MYOPIA, DISLOCATED LENSES, ID, PSYCH ABNORMALITIES, SEIZURES, THROMBOEMBOLISM
- DX:
  - PAA - INCREASED METHIONINE
  - INCREASED HOMOCYSTEINE
- TX: B6, B12, FOLATE, BETAINE, METHIONINE RESTRICTION





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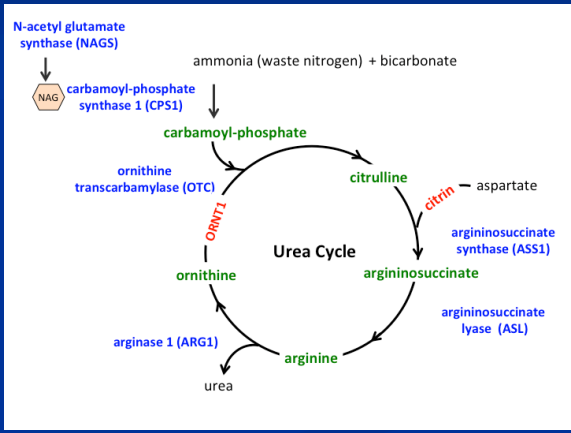
UREA CYCLE DEFECTS

- INCIDENCE: 1/30000
- SX:
  - 1ST WEEK: POOR FEEDING, TACHYPNEA, VOMITING, LETHARGY (HYPERAMMONEMIA)
  - SEIZURES
  - NEONATAL COMA
- DX:
  - HYPERAMMONEMIA
  - RESPIRATORY ALKALOSIS
  - ABSENCE OF KETOACIDOSIS
  - NORMAL/LOW BUN



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CAUSES OF HYPERAMMONEMIA

- UREA CYCLE DEFECTS
- ORGANIC ACID ABNORMALITIES
- FATTY ACID OXIDATION DEFECTS - MCAD/LCHAD
- MITOCHONDRIAL - PYRUVATE DEHYDROGENASE DEFICIENCY

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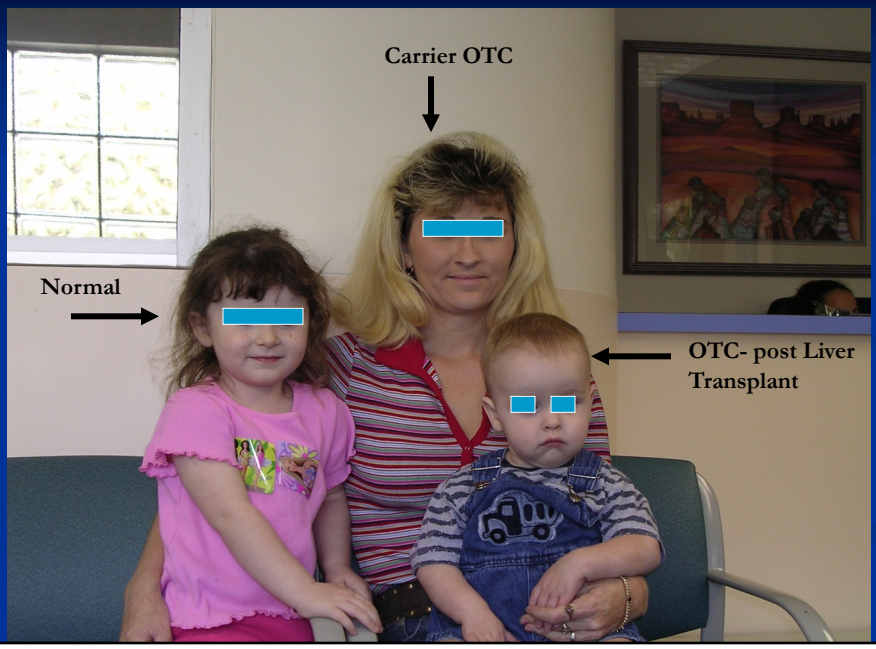
OTC



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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

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FATTY ACID OXIDATION DEFECTS

VLCAD- DIAGNOSED AT 16 MONTHS

MCAD- NBS DIAGNOSIS

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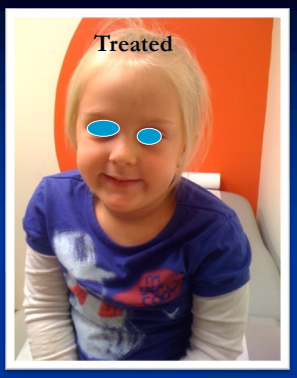
BIOTINIDASE DEFICIENCY

SX:

- SEIZURES, HYPOTONIA, ATAXIA
- DEVELOPMENTAL DELAY
- VISION PROBLEMS, HEARING LOSS
- CUTANEOUS ABNORMALITIES (E.G., ALOPECIA, SKIN RASH, CANDIDIASIS)



OLDER CHILDREN AND AND ADOLESCENTS:

- MOTOR LIMB WEAKNESS, SPASTIC PARESIS, AND DECREASED VISUAL ACUITY

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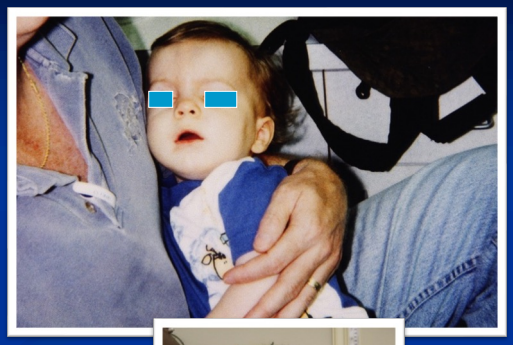
CANAVAN DISEASE

- 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



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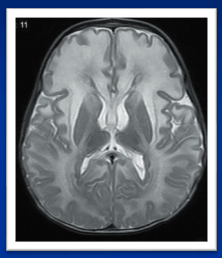
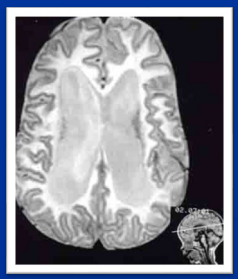
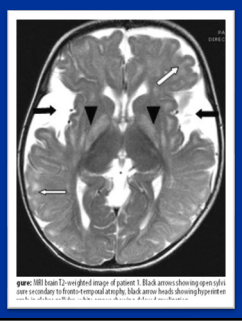
CAUSES OF MACROCEPHALY

- ALEXANDER DISEASE →
- L-2 HYDROXYGLUTARIC ACIDURIA
- CANAVAN →
- GLUTARIC ACIDURIA- 1





Canavan- demyelination with diffuse white matter changes



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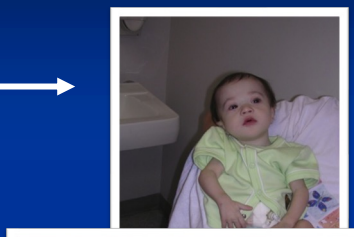
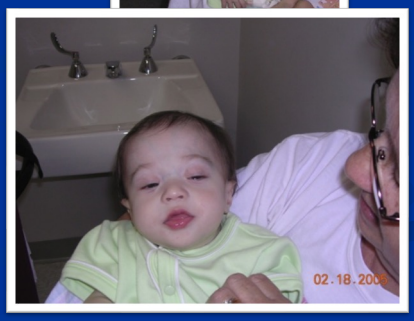
PEROXISOMAL DISEASES

- ZELLWEGER (INCREASED VLCFA)
- NEONATAL ADRENOLEUKODYSTROPHY (INCREASED VLCFA)
- REFSUM (INCREASED PHYTANIC ACID)





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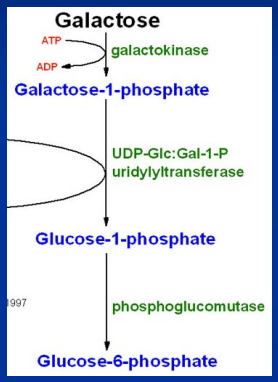
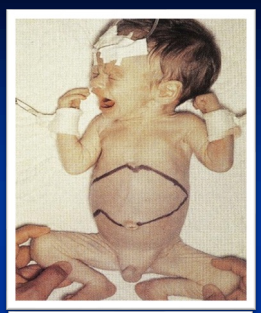
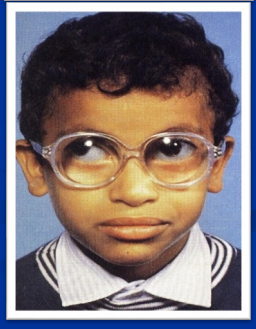
CARBOHYDRATE METABOLISM

GALACTOSEMIA

- GAL-1-P- URIDYL TRANSFERASE (GALT)
- SX:
  - VOMITING, DIARRHEA, LIVER DISEASE, CATARACTS, E. COLI SEPSIS, INFERTILITY, SPEECH DELAY
- TX:
  - LACTOSE-FREE DIET







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CAUSES OF CATARACTS

- GALACTOSEMIA
- HOMOCYSTINURIA
- FABRY DISEASE
- LOWE SYNDROME
- ZELLWEGER SYNDROME

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GALACTOSEMIA

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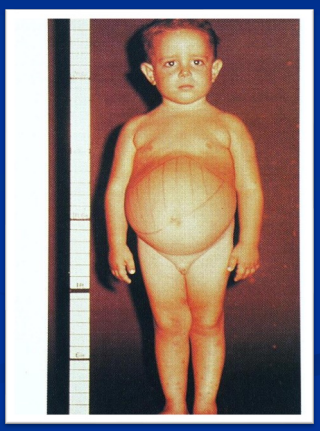
GLYCOGEN STORAGE DISEASE TYPE I (VON GIERKE)

- DEFICIENCY OF HEPATIC GLUCOSE-6-PHOSPHATASE
- 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



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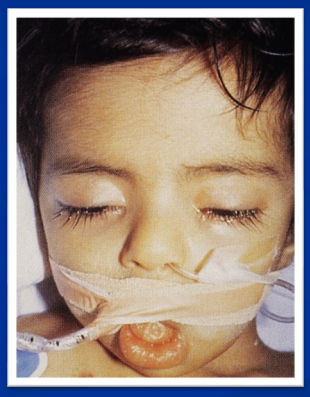
GLYCOGEN STORAGE DISEASE TYPE 2 (POMPE)

- ACID MALTASE DEFICIENCY
- SX:
  - CARDIOMEGALY, INCREASED CPK, MACROGLOSSIA HYPOTONIA
- EKG:
  - SHORT PR INTERVAL, LARGE QRS COMPLEX
- TX:
  - ENZYME REPLACEMENT- MYOZYME



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CAUSES OF CARDIOMYOPATHY

- POMPE
- GLYCOGEN STORAGE TYPE 3
- FATTY ACID OXIDATION DEFECTS
- MUCOPOLYSACCHARIDOSIS

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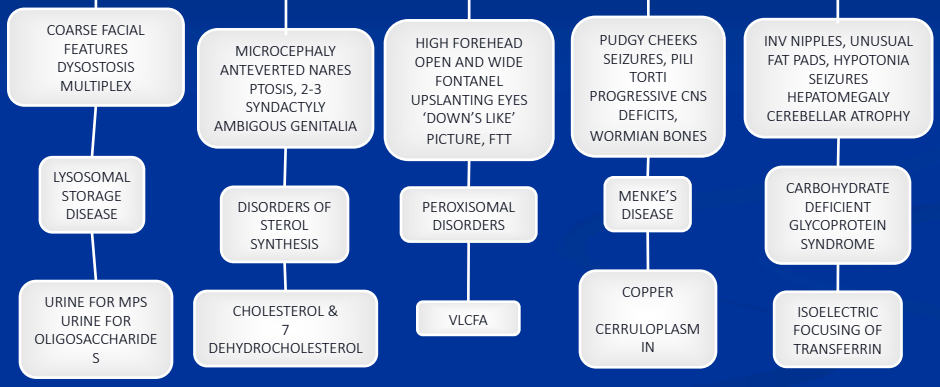
DYSMORPHIC FEATURES



- MPS – MUCOPOLYSACCHARIDOSIS
- VLCFA – VERY LONG CHAIN FATTY ACIDS

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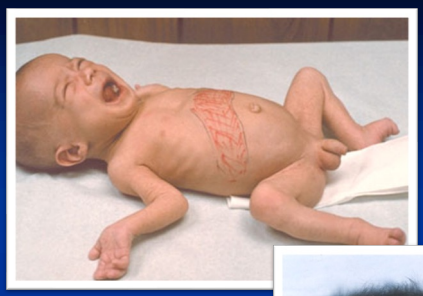
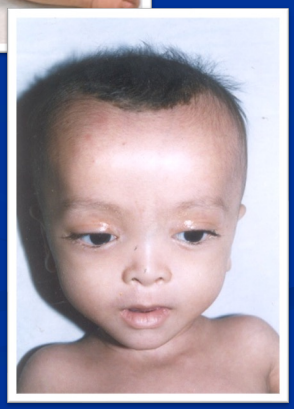
DYSMORPHIC FEATURES

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

PEROXISOMAL DISORDERS
ZELLWEGER SYNDROME

INCREASED VLCFA





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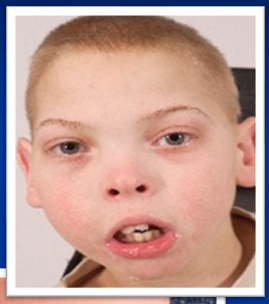
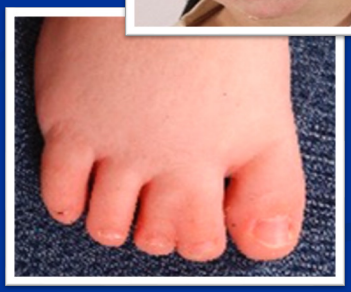
DYSMORPHIC FEATURES

MICROCEPHALY
ANTEVERTED NARES
PTOSIS, 2-3 SYNDACTYLY
AMBIGUOUS GENITALIA

DISORDERS OF STEROL SYNTHESIS

CHOLESTEROL &
7-DEHYDROCHOLESTEROL





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DYSMORPHIC FEATURES

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

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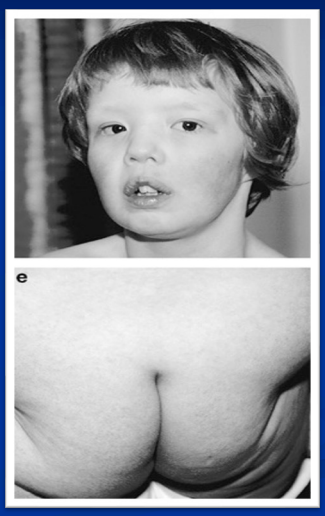
CARBOHYDRATE DEFICIENT GLYCOPROTEIN SYNDROME

↓

ISOELECTRIC FOCUSING OF TRANSFERRIN



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DYSMORPHIC FEATURES

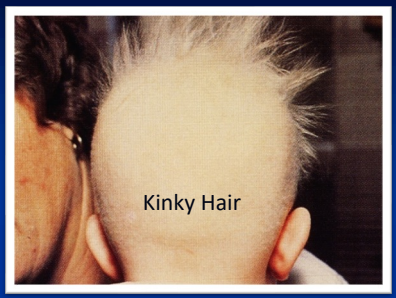
PUDGY CHEEKS SEIZURES, PILI TORTI, PROGRESSIVE CNS DEFICITS, HYPOTONIA, WORMIAN BONES, SUBDURAL HEMATOMA

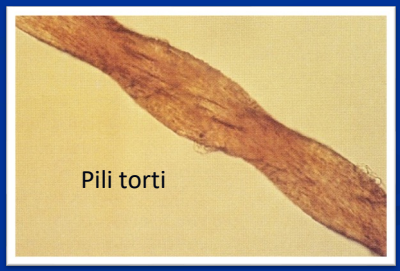
↓

MENKES DISEASE X-LINKED RECESSIVE

↓

LOW COPPER LOW CERULOPLASMIN





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DYSMORPHIC FEATURES

- COARSE FACIAL FEATURES
  DYSOSTOSIS MULTIPLEX
- LYSOSOMAL STORAGE DISEASE
- URINE FOR MPS
  URINE FOR OLIGOSACCHARIDES

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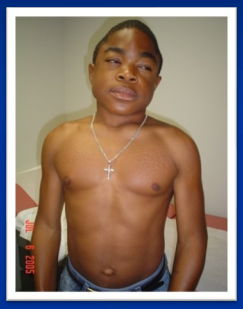
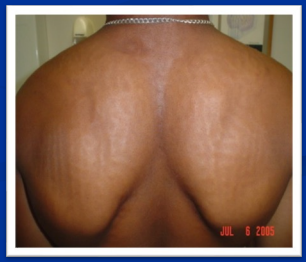
HUNTER SYNDROME (MPS II)

- X-LINKED RECESSIVE
- IDURONATE SULPHATASE DEFICIENCY
- INTELLECTUAL DISABILITY
- NO CORNEAL CLOUDING
- TX:
  - ELAPRASE ER





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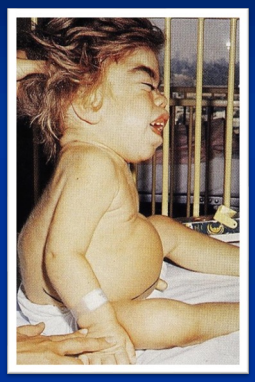
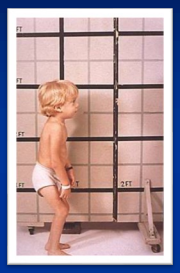
HURLER SYNDROME - MPS I

- IDURONIDASE DEFICIENCY
- SX:
  - CORNEAL CLOUDING
  - INTELLECTUAL DISABILITY
  - COARSE FACIES
  - DYSOSTOSIS MULTIPLEX
- TX:
  - ENZYME REPLACEMENT

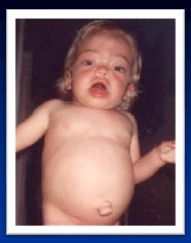


Skeletal deformities (Gibbus)

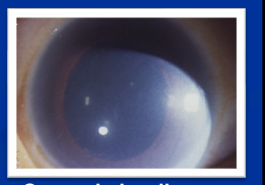


Short stature

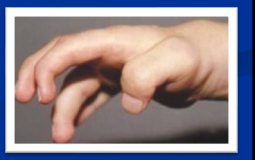
Umbilical/inguinal hernia



Hepatosplenomegaly



Corneal clouding



Carpal tunnel syndrome

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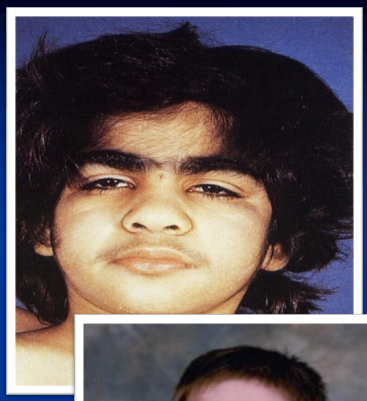
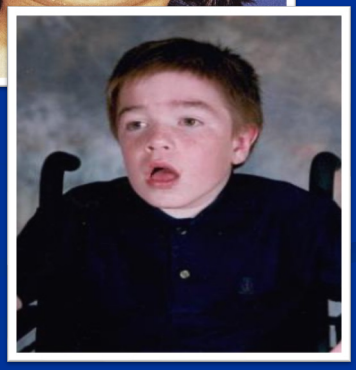
SANFILIPPO (MPS III)

- AUTOSOMAL RECESSIVE
- SX:
  - INTELLECTUAL DISABILITY
  - ADHD
  - MILD SKELETAL CHANGES
- DX:
  - HEPARAN SULFATE - URINE





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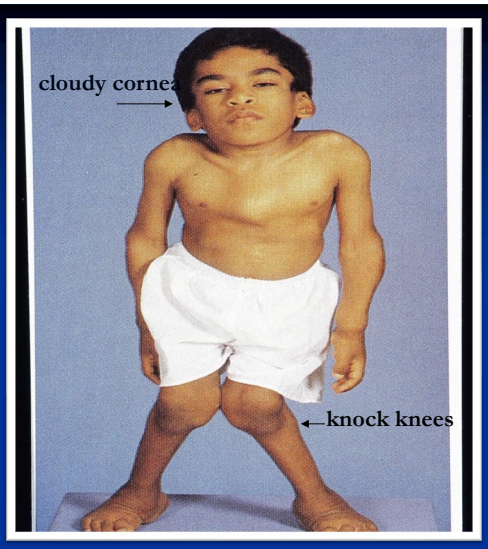

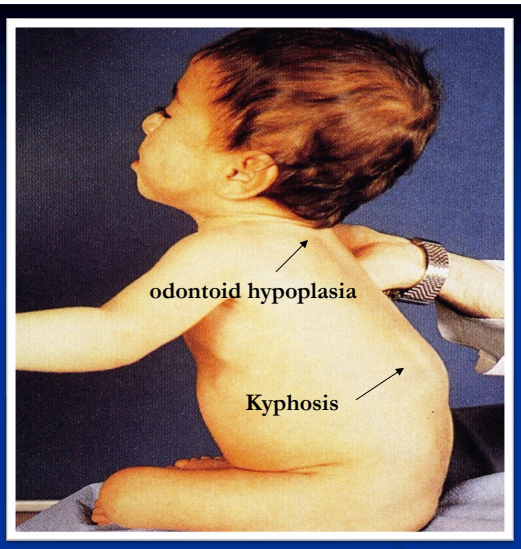

- TYPES A AND B, AUTOSOMAL RECESSIVE
- NORMAL INTELLIGENCE

MORQUIO SYNDROME (MPS IV)

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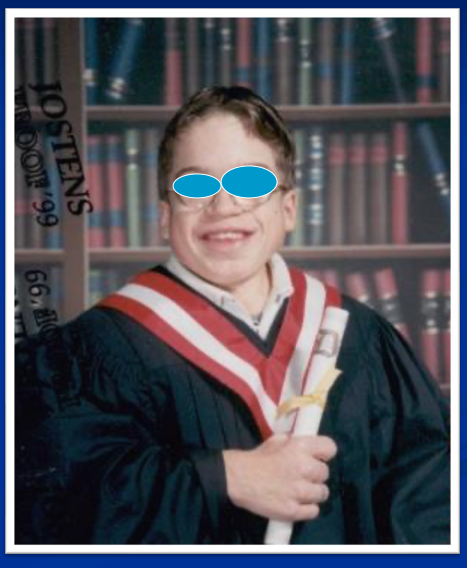
MAROTEUX-LAMY SYNDROME (MPS VI)

- ARYLSULPHATASE B DEFICIENCY
- SX:
  - ONSET 1-3 YEARS
  - CORNEAL CLOUDING
  - COARSE FACIES, JOINT STIFFNESS, SKELETAL DEFORMITIES, HEART VALVULAR DISEASE
  - NORMAL INTELLIGENCE
- TX:
  - ENZYME REPLACEMENT



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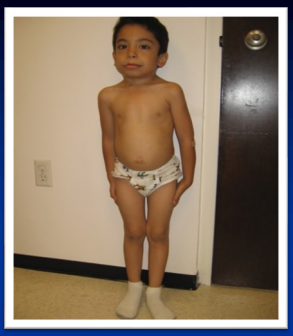
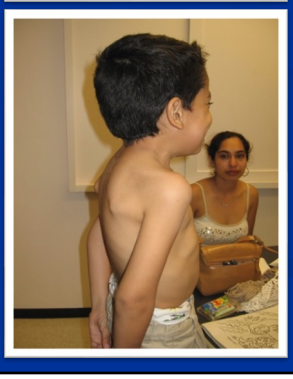
SLY (MPS VII)

- B-GLUCURONIDASE DEFICIENCY
- SX:
  - PRENATAL ONSET HYDROPS/ASCITES
  - SEVERE INTELLECTUAL DISABILITY
  - CORNEAL CLOUDING
  - HEPATOSPLENOMEGALY
  - SKELETAL CHANGES





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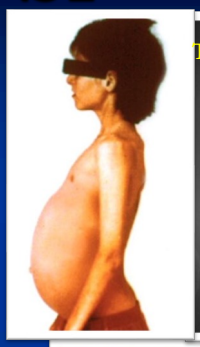
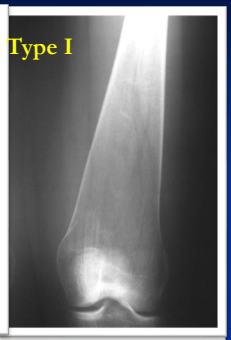
GAUCHER DISEASE

GLUCOCEREBROSIDE DEFICIENCY

CLINICAL MANIFESTATION

- TYPE I – NON-NEURONOPATHIC
  HEPATOSPLENOMEGALY, ANEMIA, BLEEDING TENDENCIES, ABDOMINAL PAIN; SKELETON: PAIN, DEFORMITIES; NO CNS INVOLVEMENT; JEWISH, 1/500- 1000
- TYPE II- NEURONOPATHIC
  CNS INVOLVEMENT, OPTHALMOPLEGIA, SPASTICITY, CNS DEGENERATION; NO ETHNIC
  HEPATOSPLENOMEGALY; RAPIDLY PROGRESSIVE IN INFANCY
- TYPE III
  MILDER COURSE WITH CNS INVOLVEMENT, OFTEN HEPATOSPLENOMEGALY





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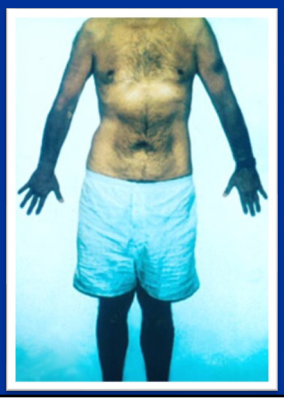
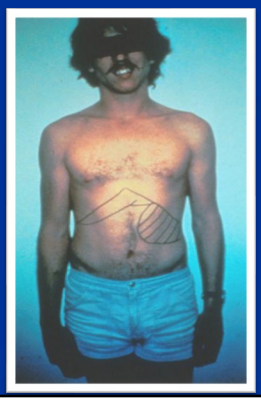
TYPE 1 GAUCHER

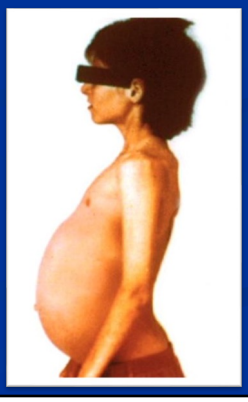
ASYMPTOMATIC 80-YEAR-OLD MAN

MILDLY AFFECTED YOUNG ADULT

SEVERELY AFFECTED GIRL







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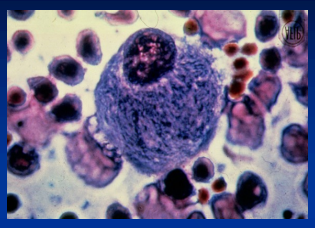
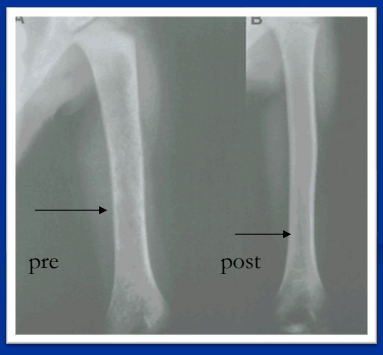
GAUCHER DISEASE

- BETA GLUCOSIDASE DEFICIENCY
- DX:
  - FOAM CELLS ON HISTO
- TX:
  - CEREZYME ERT (TYPE 1 GAUCHER)



Bone Marrow Macrophage
Engorged with Glucosylceramide



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LEUKODYSTROPHIES

METACHROMATIC:

- ARYLSULPHATASE A DEFICIENCY
- SX:
  - DEVELOPMENTAL DELAY, ATAXIA, OPTIC ATROPHY
  - NEUROREGRESSION (1-2Y)
- TX:
  - SYMPTOMATIC

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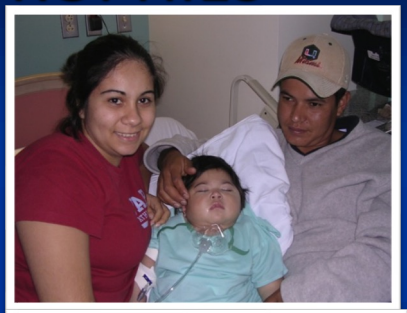
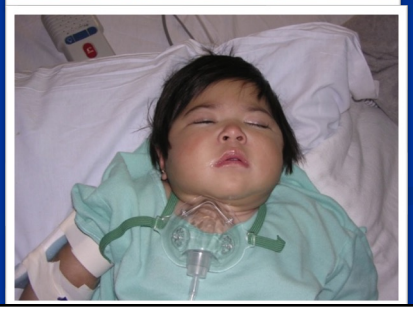
LEUKODYSTROPHIES

KRABBE:

- GALACTOCEREBROSIDASE DEFICIENCY
- SX:
  - ONSET <6 MO
  - HYPERTONIA, IRRITABILITY, OPTIC ATROPHY, INC CSF PROTEIN, ABNORMAL MRI
- TX:
  - SYMPTOMATIC





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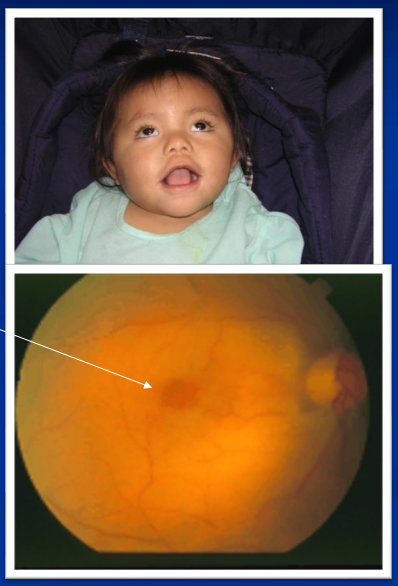
TAY SACHS DISEASE

- HEXOSAMIDASE A DEFICIENCY
  - INABILITY TO DEGRADE GM2 GANGLIOSIDE
- SX:
  - 6-12 MONTHS: SLOWING DEVELOPMENT, HYPERACUSIS, APATHY, CHERRY RED SPOT, SEIZURES, BLINDNESS, SPASTICITY
  - DEATH BY 2-5 YEARS
- LATE ONSET WITH RESIDUAL ACTIVITY
  - MOTOR NEURON DYSFUNCTION , ATAXIA BUT NORMAL IQ AND VISION (ALTHOUGH 1/3 HAVE PSYCHOSIS)



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CAUSES OF CHERRY RED MACULA

- TAY SACHS DISEASE
- SANDHOFF
- GM 1 GANGLIOSIDOSIS
- NIEMANN-PICK DISEASE
- SIALIDOSIS
- MUCOLIPIDOSIS

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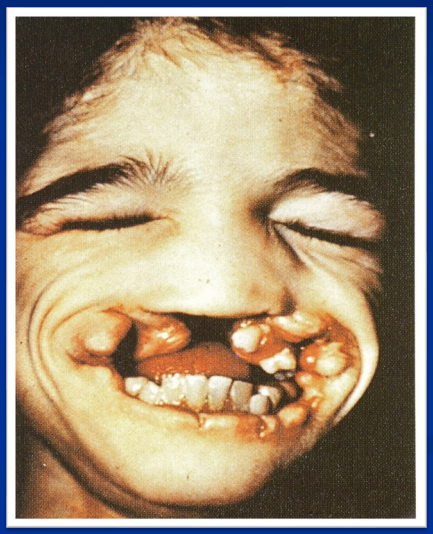
PURINE/PYRIMIDINE

LESCH-NYHAN:

- X-LINKED RECESSIVE
- HGPRT DEFICIENCY
- SX:
  - NORMAL AT BIRTH, MR, CHOREIFORM MOVEMENTS, SELF MUTILATION, GOUT.
- DX:
  - INCREASED URIC ACID
  - MRI: BASAL GANGLIA ABNORMALITIES
- TX:
  - ALLOPURINOL
  - SYMPTOMATIC



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OVERVIEW OF METABOLIC DISORDERS

- CLASSIFICATIONS
- CLINICAL PRESENTATION
- NEWBORN SCREEN
- COMMON METABOLIC DISORDERS
- PRINCIPLES OF TREATMENT

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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

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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 AND PROMOTE DIURESIS.
- VITAMINS
  - BIOTIN, VITAMIN B6, COBALAMINE, THIAMINE, OR RIBOFLAVIN
- HEMODIALYSIS FOR LIFE-THREATENING METABOLIC DISTURBANCES

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LONG TERM MANAGEMENT

- AUGMENT THE ACTIVITY OF AN ENZYME
  - 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
  - GAUCHERS, HURLER, POMPE, MPS IV, HUNTER
- ORGAN TRANSPLANT
  - LIVER TRANSPLANT IN HEREDITARY TYROSINEMIA AND OTC

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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

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