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EPNS Training Course 2017

Chronic presentations
of Infantile Metabolic Encephalopathies

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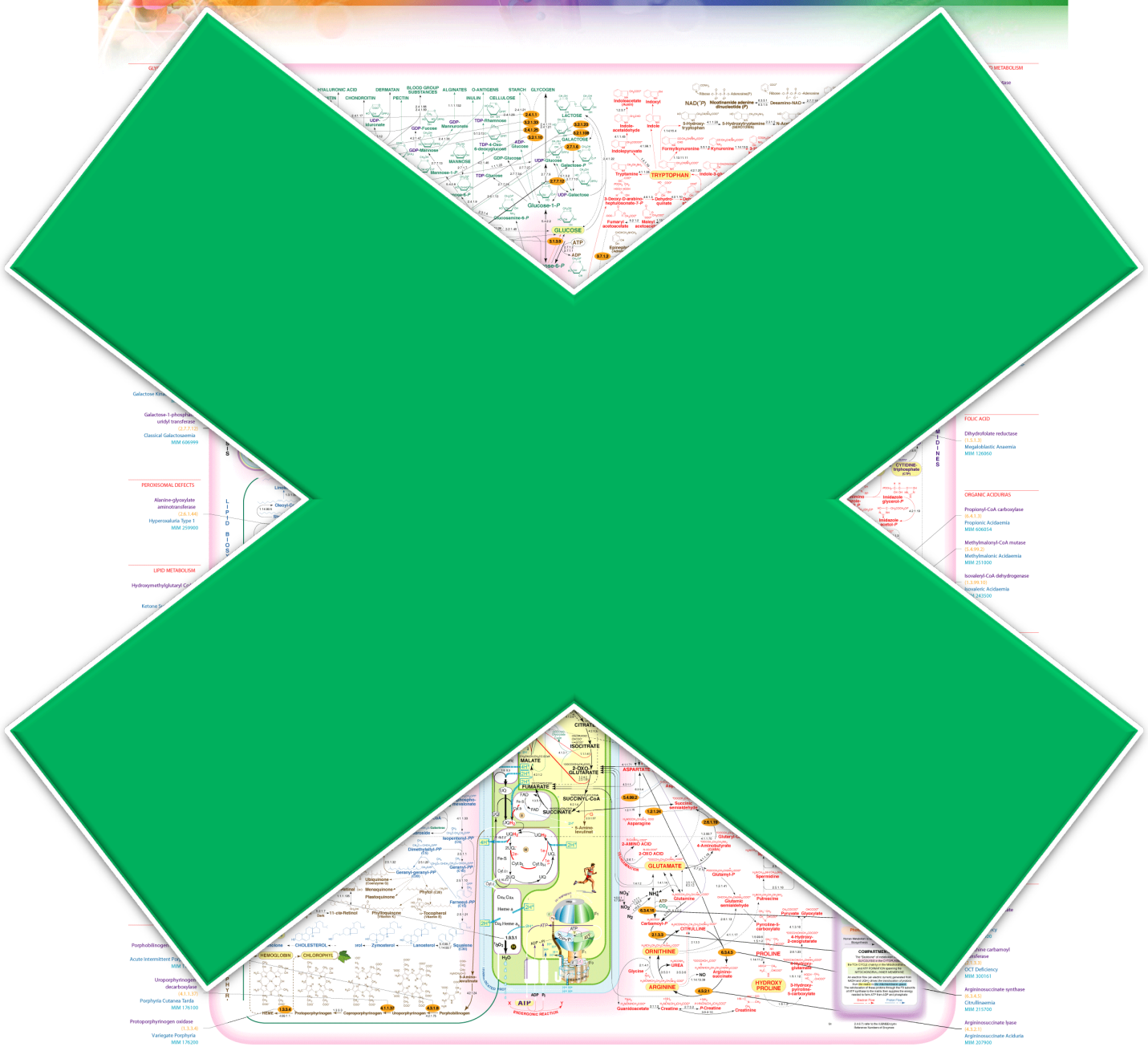
Overview – learning objectives

- Pathophysiological classification
- Epidemiology
- Causes - genetics
- Clinical features
- Developmental delay vs. regression
- Specific disorders/groups of disorders
- Take home messages

Inborn Errors of Metabolism

EPNS



Pathophysiologic classification

Group 1: disorders that give rise to intoxication
(acute or chronic)

Group 2: disorders involving energy metabolism

Group 3: disorders involving complex molecules

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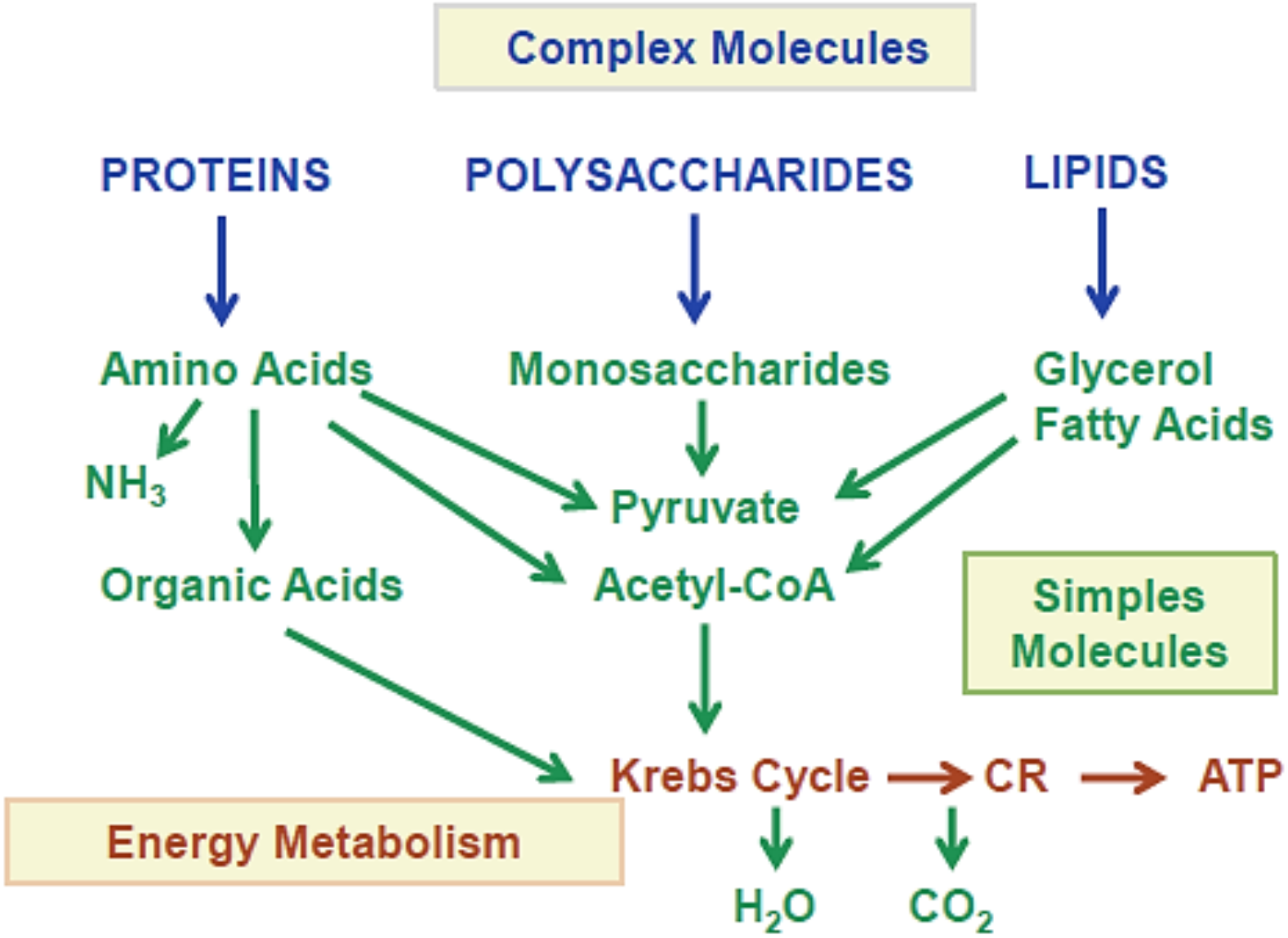

Complex Molecules
PROTEINS
POLYSACCHARIDES
LIPIDS
Amino Acids
Monosaccharides
Glycerol
Fatty Acids
NH3
Pyruvate
Organic Acids
Acetyl-CoA
Simples Molecules
Krebs Cycle
CR
ATP
Energy Metabolism
H2O
CO2

Group 1 (intoxication)

- Aminoacidopathies (PKU, tyrosinemia etc.)
- Organic acidurias (MMA, IVA, PA etc.)
- Urea cycle disorders (OTC etc.)
- Sugar intolerances (galactosemia, hereditary fructose intolerance)
- Metal disorders
- Porphyrias

Group 2: Inborn errors of intermediate (energy) metabolism

Cytoplasmic energetic processes

- Glycolysis
- Glucogenesis
- Gluconeogenesis
- Hyperinsulinisms
- Creatine pathways
- Pentose phosphate pathways

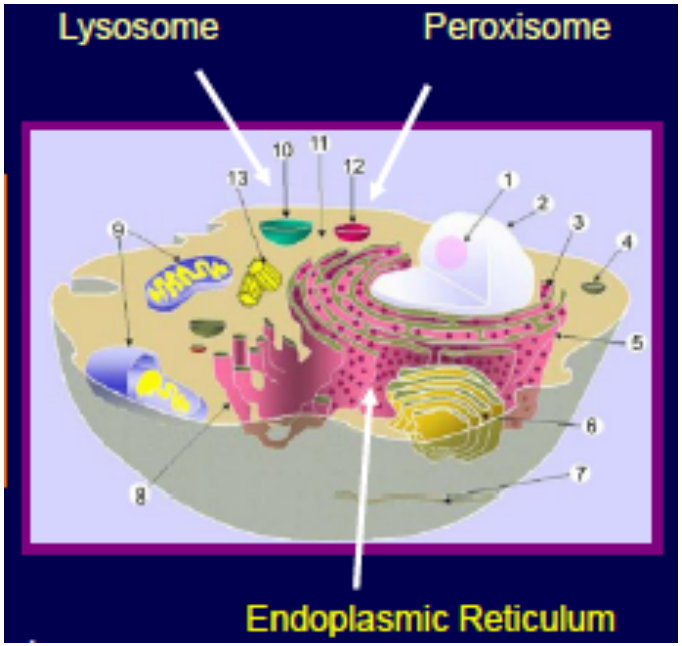
Mitochondrial

- Respiratory chain
- Krebs cycle
- Pyruvate oxidation
- Fatty acid oxidation
- Ketone bodies

Group 3:
Cellular organisms-complex molecules

- Lysosomal
- Peroxisomal
- Glycosylation
- Cholesterol synthesis

✓ *Some of them are treatable*



Group 3 (complex molecules)

- Cellular organelles (trafficking, processing)
- Disturbed synthesis or catabolism of complex molecules
- Embryo-fetal development: possible interference
- No provocative circumstances
- Permanent symptoms independent of the diet
- Storage disorders (lysosomes)
- Specific diagnostic methods (substrates, enzyme assays, molecular analyses)
- Enzyme replacement & substrate reduction treatments

Common clinical presentations
of infantile metabolic encephalopathies

- Acute symptoms in the neonatal period
- Later onset acute & recurrent attacks
  (coma, ataxia, vomiting, acidosis)
- Chronic & progressive disorders
  (neurological, muscular, digestive)
- Specific & permanent organ dysfunction
  (i.e. cardiomegaly, hepatomegaly, lens dislocation)

Clinical features associated with IME

Examination

- Growth
- Appearance
- Organomegaly
- Smell
- Neurological findings

Growth

- Failure to thrive
- Abnormal head circumference
  - **microcephaly** *(sulfite oxidase deficiency, maternal PKU, CDGs, as a result of non-specific damage)*
  - **macrocephaly** *(Canavan, L-2 hydroxyglutaric aciduria, Krabbe, GA I, Tay-Sachs)*

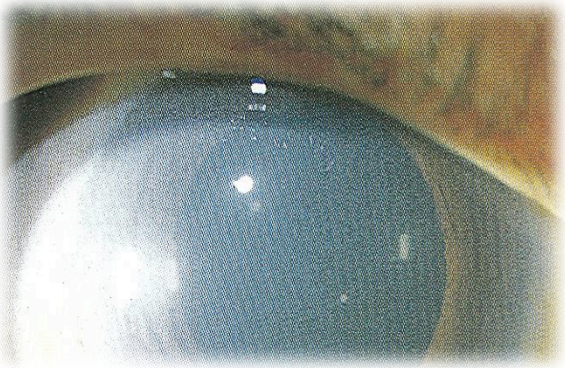
Appearance

- Eyes
- Hair
- Skin
- Dysmorphism

Eyes

Cataract

- Peroxisomal
- Homocystinuria
- Gyrate atrophy
- Galactosaemia

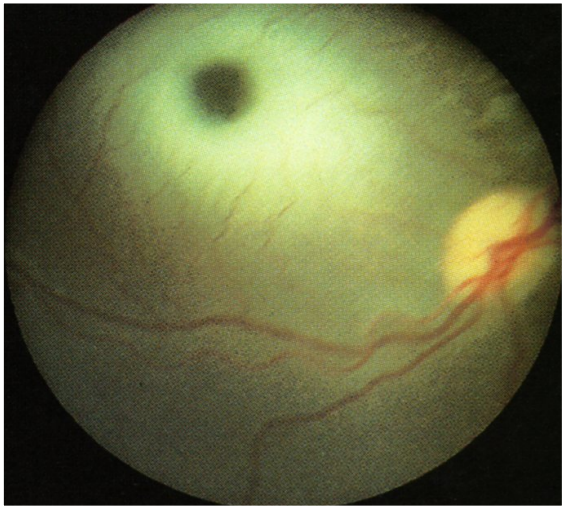


Corneal clouding

- MPSs

Cherry red spot

- Neurolipidoses



Hair

Coarse

- MPSs

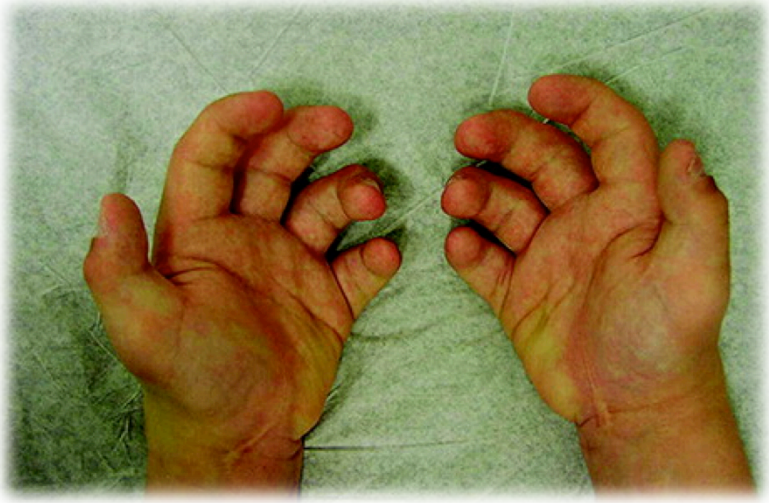
Kinky

- Menkes

Skin

Thickened, coarse

- MPSs
- Refsum's disease

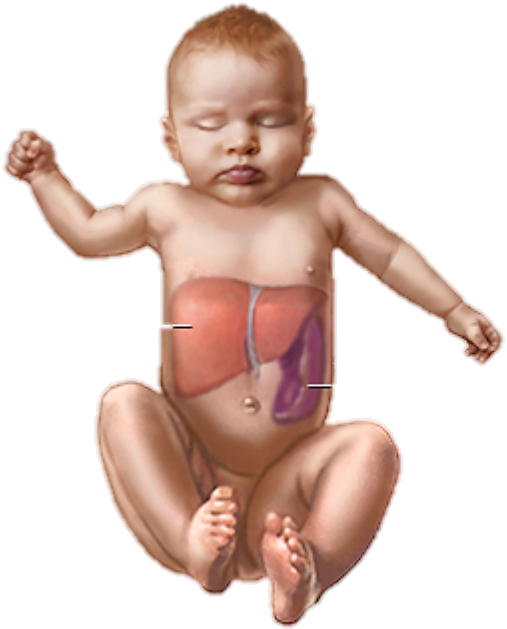


Dysmorphism

- Smith-Lemli-Opitz
- CDGs
- MPSs
- Menkes
- Peroxisomal

Organomegaly

- Gaucher
- NPB, NPC
- Other storage disorders



Smell

Sweaty feet

- Isovaleric aciduria

Maple syrup urine

- MSUD

Neurological findings

- Developmental Delay - Regression
- Hypotonia *(muscle disease, initial phase of neurological regression)*
- Spasticity *(neurodegenerative disorders)*
- Dystonia *(neurotransmitter, mitochondrial, GA I, LSDs, Wilson's, GLUT-1)*
- Ataxia *(Refsum's, GLUT-1, LSDs)*
- Stroke *(OTC, organic acidurias, Fabry, CDG, homocystinuria, mitochondrial)*
- Peripheral neuropathy *(LSDs, Refsum)*

Developmental Delay

the hallmark of static encephalopathy as the key clinical feature of IMEs

Cause of DD in the literature

Causes	%
Chromosomal abnormalities	4-28
Recognisable syndromes	3-7
Known monogenic conditions	3-9
Structural CNS abnormalities	7-17
Complications of prematurity	2-10
Environmental/teratogenic	5-13
“Cultural-familial” mental retardation	3-12
Provisional unique, monogenic syndromes	1-5
Metabolic/endocrine causes	1-5

IME as a cause of DD

- Not common cause of pure DD – 1%
- Usually other features suggesting IME

However…

some IME will present as pure DD!

History

- **Birth & prenatal**
  - Birth often normal
- **Family history**
  - Previous neonatal death
  - Parental consanguinity

History

- **Accompanying unusual episodes**
- **Unusual behavior**

DD

- **Regression?**
- Single domain
  - motor
  - language
- Multiple domains

Regression

- A period of normal development followed by loss of skills
- May follow a viral illness
- May follow minor head injury
- Strongly suggestive of IME

Metabolic causes of regression

- Disorders associated with intermediate metabolism: deficient energy production *(i.e. mitochondrial)*
- Organic acidurias *(i.e. GA I)*
- Copper metabolism disorders *(Wilson, Menkes)*
- Leukodystrophies
- LSDs
- Peroxisomal

Static encephalopathies

Multisystem diseases with major neurological involvement:

- Cholesterol synthesis disorders (SLO)
- Congenital disorders of glycosylation (CDGs)
- Glucose transporter deficiency (GLUT-1)

Cerebral palsy "plus" syndromes

Problems in interpreting clinical features

- ✓ Early fatal disease before cerebral maturation has occurred
- ✓ Extremely long standing disease where it is unclear if there is regression
- ✓ Abrupt onset confused with infectious diseases
- ✓ Intercurrent illness, seizures or drug therapies affect assessment
- ✓ Manifestations of earlier non-progressive lesions evolve

Further Lecture's Outline

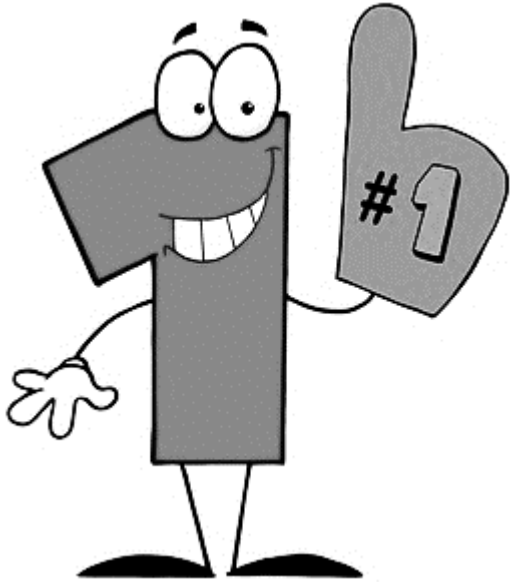
Group of disorders

i. Aminoacidopathies
ii. Mitochondrial disorders
iii. LSDs
iv. Peroxisomal disorders
v. CDGs

Single entities

i. SLOS
ii. GLUT-1 deficiency

Aminoacidopathies



Phenylketonuria (PKU)

- **Enzyme defect**: phenylalanine hydroxylase (12^{th} chromosome), more than 400 mutations
- **Incidence**: average 1:10,000 (highest incidence in Turkey, 1: 4,000)

Phenylketonuria (PKU): variants

1. **Classical phenylketonuria** (complete or near complete enzyme deficiency): phenylalanine levels above **20 mg/dL** (<1200 mmol/L) require diet therapy

2. **Atypical phenylketonuria** (partial enzyme deficiency): (enzyme activity 1-5%) require partial diet therapy

3. **Benign phenylketonuria** - phenylalanine levels below **10 mg/dL** (<600 mmol/L) no clinical findings, not requiring diet therapy

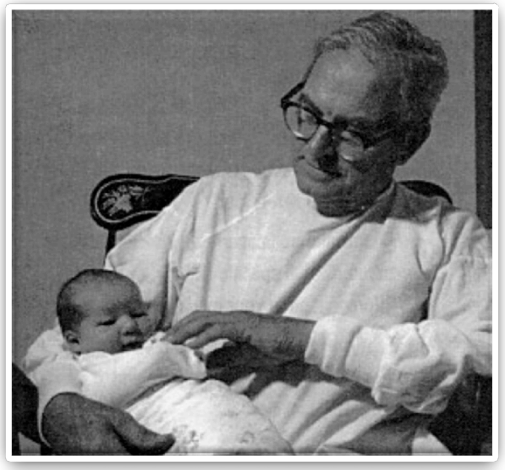
4. **Malignant phenylketonuria** - Tetrahydrobiopterin (BH4=cofactor of phenylalanine hydroxylase): Severe neurologic findings, **does not respond to diet therapy.** Dopamine and setotonin may be helpful

Phenylketonuria (PKU): Clinical findings

- Severe brain damage, progressive motor-mental retardation
- Spasticity
- Convulsions
- Self-mutilation
- Light colored skin and eye (yellow hair, blue eyes; tyrosine deficiency)
- Mouse-like odor in urine and sweat

Phenylketonuria: diagnosis

- High phenylalanine and low tyrosine levels
- Ferric chloride test gives green color in urine (not reliable)
- Neonatal screening: Guthrie-card (taken between **3rd** and **7th** days of life)



Phenylketonuria: therapy

- Phenylalanine restricted diet, supplementation of tyrosine, essential amino acids and trace elements

Goals of the therapy:

- **0-10 years**: phenylalanine values: 0.7-4 mg/dL
- **11-16 years**: phenylalanine values: <15 mg/dL
- **16+ years**: phenylalanine values: <20 mg/dL

Pregnant mothers with PKU: phenylalanine values < 7mg/dL

Prognosis: with immediate and efficient treatment, normal development and intelligence

Maternal PKU= phenylketonuric fetopathy

- Normal phenylalanine levels
- Microcephaly
- Cardiac defects
- Motor-mental retardation
- No therapy

Classical **Homocystinuria**

- **Enzyme defect**: Cystationine-ß-synthase
- **Mechanism**: Accumulation of homocysteine (collagen disorder)
- **Clinical findings**: Progressive disease, usually starting with school age

✓ Marfan-like appearance (arachnodactyly)

✓ Progressive myopia (the earliest finding**)**

✓ **Lens dislocation**

✓ Epilepsy

✓ Mental retardation

✓ Osteoporosis

✓ **Thromboembolism !!!**

Homocystinuria

- **Diagnosis:** High **methionine,** high **homocysteine** (N: 0-3.5 µmol/L) and low cysteine levels
- **Therapy:** Pyridoxine (Vit. B6): 50-1000 mg/day + folic acid 10 mg/day.
- If this fails diet + betaine (100 mg/kg) up to 3X3 g
- **Goal:** Keep homocysteine <3.0 µmol/L

MILD HYPERHOMOCYSTEINEMIA
Causes

- Methylene tetrahydrofolate reductase (MTHFR) polymorphism, thermolabile variant, homozygosity, up to 5% in Europeans, 60% in Asians
- Heterozygosity for cystationine-ß-synthase
- Endogenous and exogenous disorders of folic acid metabolism
- Vitamin B12 deficiency

MILD HYPERHOMOCYSTEINEMIA

Clinical findings:

- **Premature vascular disease** in the 3rd and 4th decade (infarctions, thrombosis, embolism)

Maternal hyperhomocysteinemia:

Congenital defects

- Neural tube defects
- Cardiac output defects
- Renal defects
- Pyloric stenosis?

Mitochondrial disorders

Mitochondrial Disorders

Any system

Any inheritance

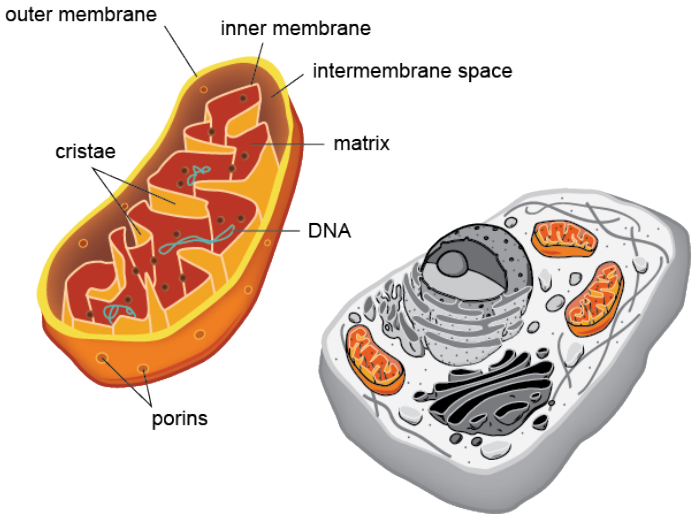
Any age

Genetics of mitochondrial diseases

Mutations within mtDNA

- MELAS
- Kearns-Sayre
- MERFF
- NARP

Nuclear DNA mutations



Genetics of mitochondrial DNA maintainance
(mtDNA depletion or multiple deletions within mtDNA)

Gene	Age of onset	Major CNS features	Organ involvement	Inheritance
mtDNA replication				
POLG	Infancy-adult	Ataxia, seizures, dementia Blindness, PEO, neuropathy, Developmental delay, ptosis	Brain, liver, muscle	Recessive and dominant
POLG2*	Infancy-Adolescent	PEO, migraine, hypotonia, Developmental delay, Seizures, blindness	Brain, liver, muscle	dominant
C10rf2	Infancy	Seizures, PEO, psychosis, MR, ataxia, hypotonia	Brain, liver	recessive
Nucleotide Pool Maintenance				
DGUOK	Neonatal-Adolescent	Dystonia, nystagmus, developmental delay	Brain, liver	recessive
TK	Infancy-Child	Seizure, PEO	Brain, muscle	recessive
RRM2B	Neonatal	Microcephaly, hypotonia, PEO, MR, Hearing loss	Muscle, kidney	recessive
TYMP	Adolescent-adult	Leukodystrophy, PEO, ptosis, encephalopathy, neuropathy	Brain, GI, Peripheral nerve	recessive
SLC25A4	Adult	PEO	Muscle	dominant
SUCLG1/SUCLA2	Neonatal-infancy	Dystonia, hearing loss, encephalopathy, PEO	Brain, muscle	recessive
Unknown Function				
MPV17	Neonatal-adult	Ataxia, neuropathy, dystonia Hypotonia, encephalopathy, leukodystrophy	Liver, brainmuscle	recessive

Epidemiology of mitochondrial diseases

- As a group ➔one of the most common IEMs
- Total minimal birth prevalence (for both mtDNA and nuclear DNA) around 1 in 5,000
- In two large pediatric studies (Sweden & Australia): minimum birth prevalence 4.7 per 100,000 & 5.0 per 100,000
- In both studies: 15% of children ➔ mtDNA mutation
- Recent estimations (report from northern England) ➔ approximately 1 in 200 live births possess a pathological mtDNA mutation
- It is not clear why the high prevalence of pathological mtDNA mutations does not translate into higher disease prevalence

Onset of mitochondrial disease

- Median age of 7 months in one large study and 44 months in another (range 1 mo to 18 y)
- **Nuclear mutations:** the majority (83%)
- A small but larger proportion and diversity of mtDNA-derived diseases compared to neonatal onset disorders
- Patients with likely nuclear genome mutations present earlier, while patients possessing mtDNA mutations present later in life

CNS manifestations of mitochondrial diseases

	Neonatal	Childhood
Neurological	Unexplained encephalopathy Psychomotor delay Myopathy Hypotonia Seizures Involuntary movements Microcephaly Hearing loss Ataxia	Encephalopathy (illness, drugs) Global developmental delay Myopathy Hypotonia Seizures Involuntary movements Microcephaly Hearing loss Ataxia Myoclonus Peripheral neuropathy Migraine Absent deep tendon reflexes Stroke-like events Dysarthria Psychiatric disorders
Opthalmological	Optic atrophy Ptosis Nystagmus Ophthalmoplegia/paresis	Optic atrophy Ptosis Nystagmus Lack of smooth pursuit Ophthalmoplegia/paresis Retinal degeneration

Signs of mitochondrial disease

- **Both grey and white matter**
- **Other suggestive signs**
  - Cardiomyopathy
  - Ocular signs (retinitis pigmentosa, cataract, ptosis)
  - Muscle disease
  - Haematological
  - Liver disease

The A to Z of Mitochondrial Symptoms and Signs

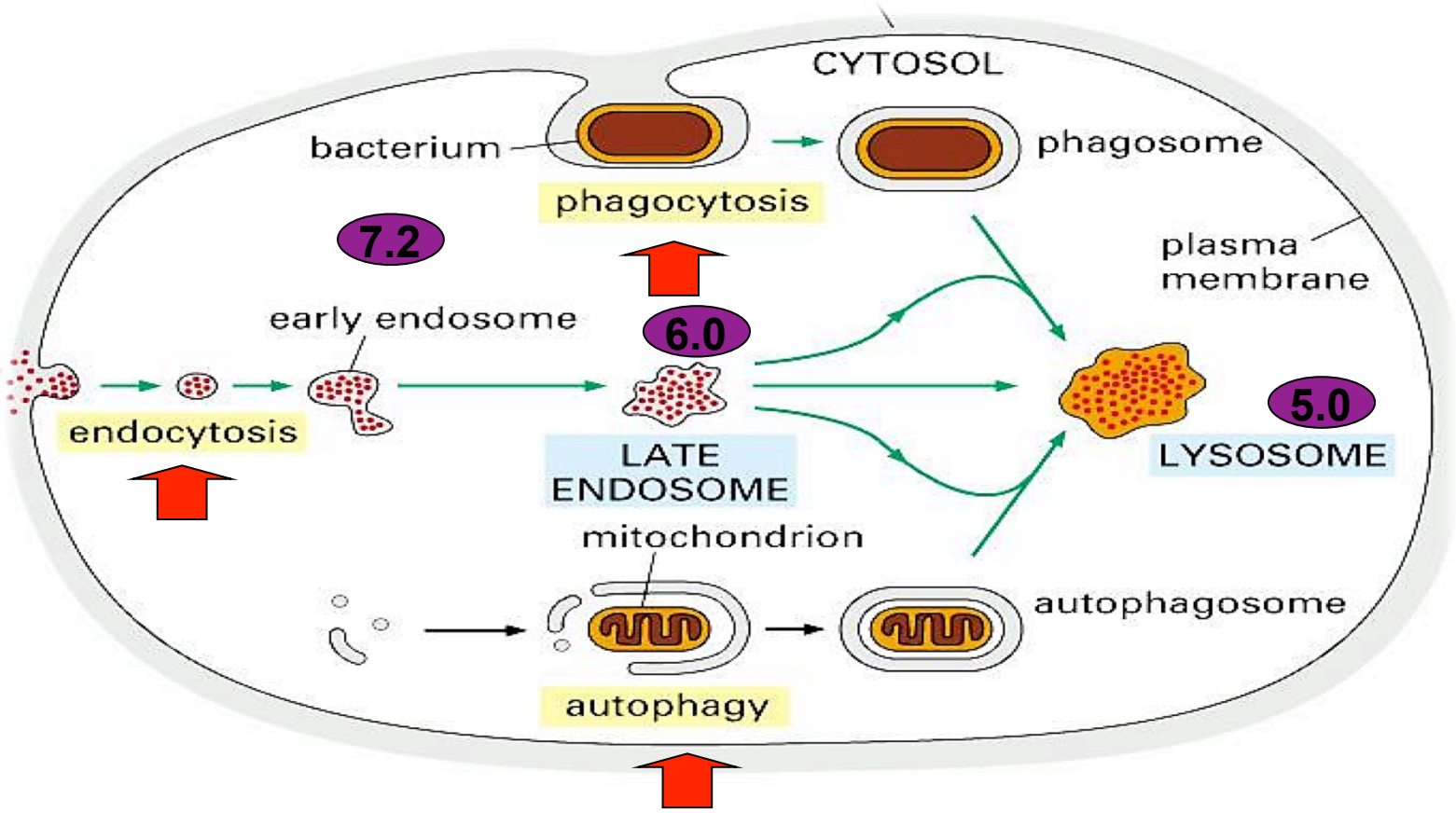
Aminoglycoside deafness	Neuropathy
Bone marrow dysfunction	Optic atrophy
Cardiomyopathy	**Progressive** organ involvement
Diabetes	Questionable diagnosis
Episodic vomiting	Retinitis pigmentosa
Fever	Seizures
Gastrointestinal Motility	Tachypnea
Hepatomegaly	Unexplained assoc symptoms
Idiopathic dystonia	Vascular abnormalities
Jaundice	Wasting
Kidney dysfunction	Xertional myoglobinuria
Lipomas	Yucky outlook
Malformations	Zestless

Leigh Disease or Leigh-like Disease

- Mutations in both nuclear (80%) as mtDNA (20%)
- Can be slow onset - regression
- Episodic hyperventilation
- Basal ganglia changes

Lysosomal Storage Disorders

LSDs


CYTOSOL
bacterium
phagosome
phagocytosis
7.2
plasma membrane
early endosome
6.0
endocytosis
LATE ENDOSOME
5.0
LYSOSOME
mitochondrion
autophagosome
autophagy

Epidemiology of LSDs

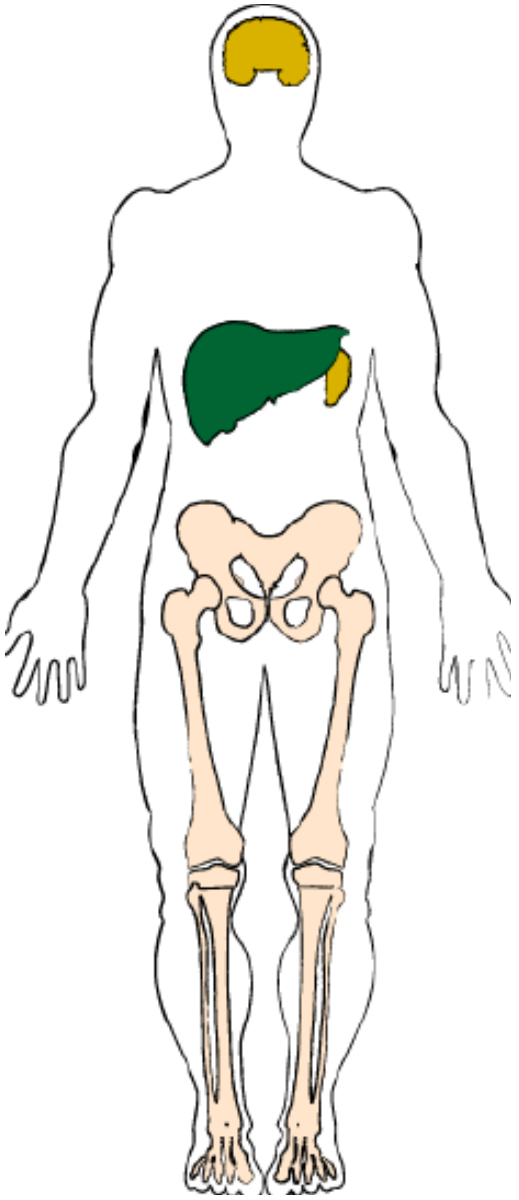
- Approximately 1 in 5000 to 8000 births in the United States, Europe and Australia
- Collectively LSDs affect a considerable portion of the population (prevalence ranging from **12 to 25 per 100,000 live births**)
- **> 50 different genes** identified
- Large number of mutations for most disorders - wide clinical spectra

The main clinical manifestations of LSDs:

the CNS, the joints, the bones, the liver and spleen

Other manifestations include:

the eyes, the heart and the skin



Ideal way to approach the neurology of LSDs but also other organelle disorders

Clinical **symptoms and signs?**

Specific diseases or **group of diseases?**

"Splitters": **symptoms & signs**

i. **Only** neurological involvement

ii. **No** neurological involvement

iii. **Primary** neurological involvement

iv. **Secondary** neurological involvement

1

Only neurological involvement

The presence of pure neurological signs and symptoms without additional somatic features *(i.e. coarse facies, organomegaly, bone dysplasias)* justifies searching for:

- **GM1 & GM2** gangliosidosis
- **MLD**
- **CNLs**
- **Krabbe** disease

2

No neurological involvement

- **Gaucher disease type 1**
- **MPS** IV & VI

However:

✓ patients with **GD1** have higher risk for: impaired saccades, Parkinson disease, schizophrenia, mood disorders & dementia

✓ Patients with **MPSs IV** & **VI** may develop: obstructive hydrocephalus from spinal cord compression (with all associated symptomatology)

Primary neurological involvement

Symptoms & signs related to:

i. **CNS dysfunction**
ii. **PNS dysfunction**
iii. **Vision**
iv. **Hearing**

CNS dysfunction

- Developmental delay, mental retardation or regression *(most LSDs)*
- Spasticity *(most LSDs with regression)*
- Dystonia-parkinsonism *(GM2, NPB, NPC)*
- Ataxia *(GM2, NPC)*
- Myoclonus *(GD2 & 3, GM2, sialidosis I)*
- Seizures *(NCL,sialidosis, presence of cortical involvement on MRI)*
- Craniosynostosis *(alpha mannosidosis, GD3, MPS II, ML II)*
- Psychosis *(GM2, MLD, NPC)*
- Intracranial hypertension *(MPSs, cystinosis, Pompe)*

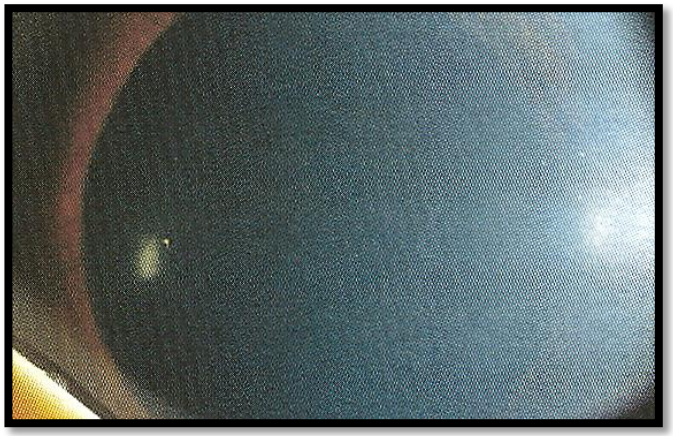
Eye involvement

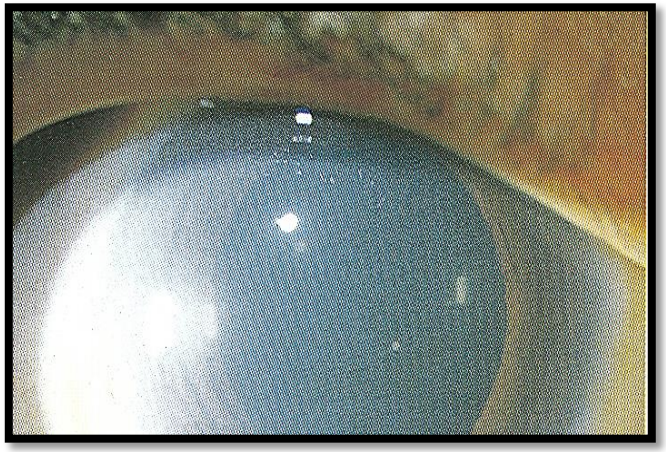
- **Cornea, lens, sclera, retina & nerve**
  - Cataract
  - Other corneal pathology
  - Glaucoma
  - Retinopathy
  - Optic atrophy
  - Cherry-red spot

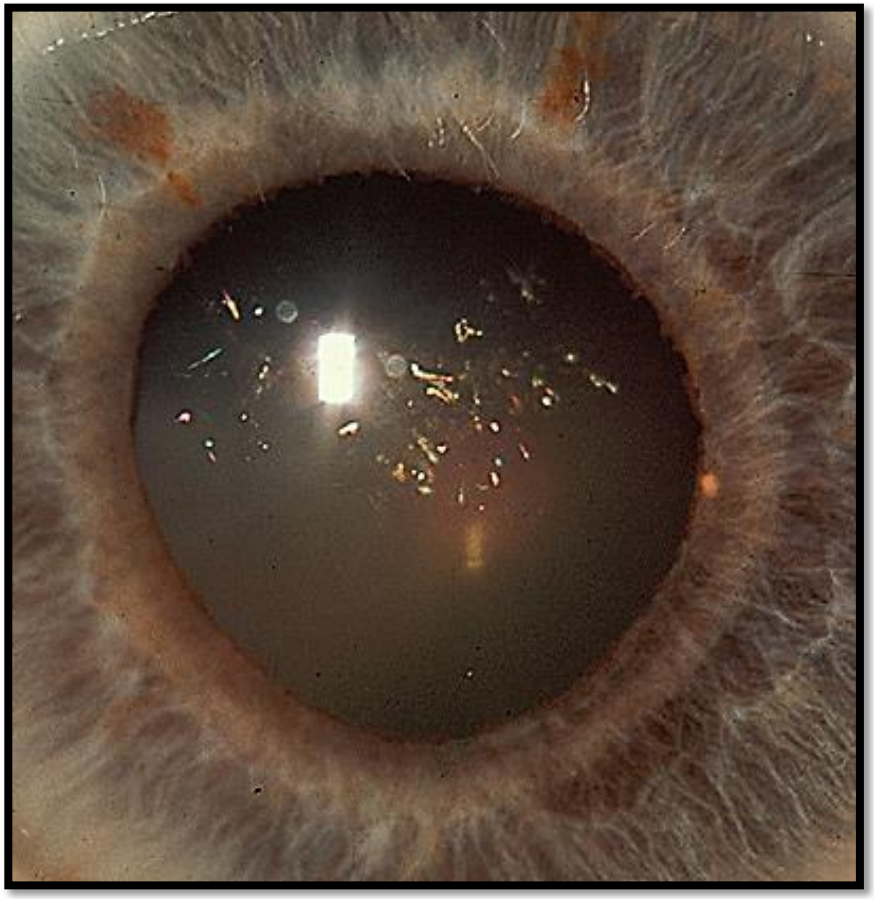
- **Eye movement disorders**
  - Supranuclear opthalmoplegia & abnormal saccades
  - Vertical gaze paresis
  - Squint

Cataract

(Fabry, galactosialidosis, MPS I & VI, ML IV)

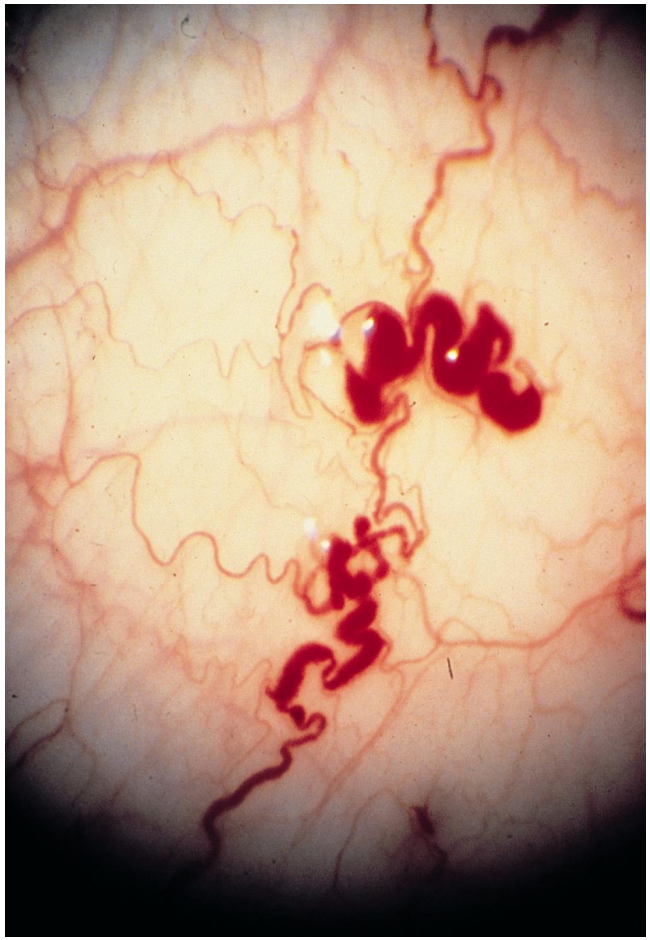


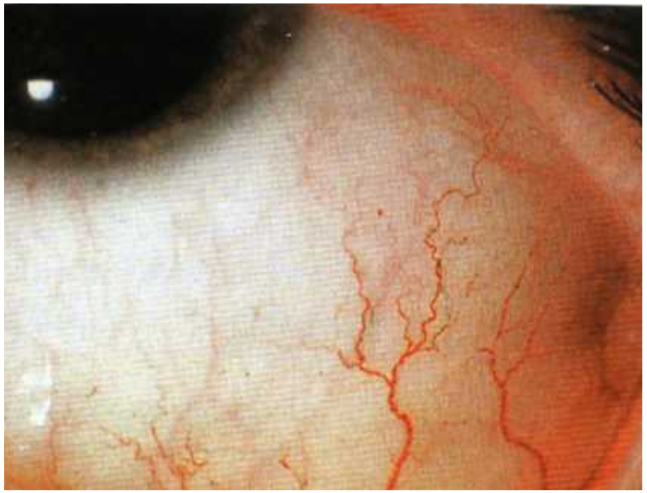


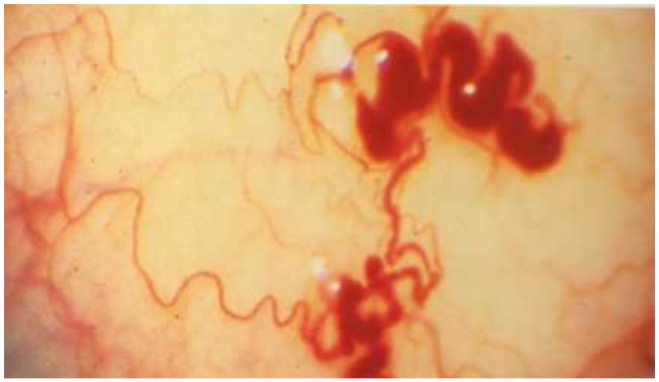


Whorl-like keratopathy

(Fabry)



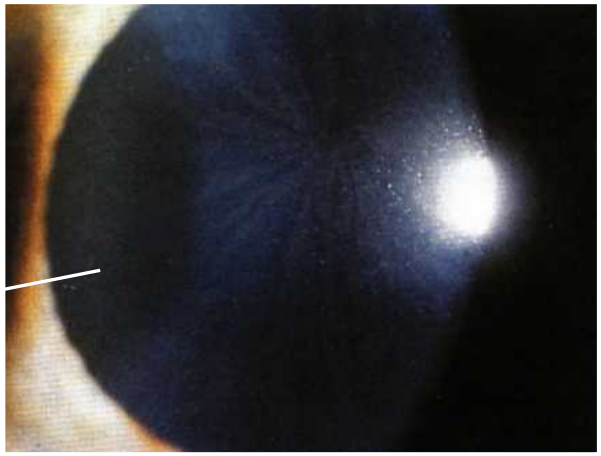


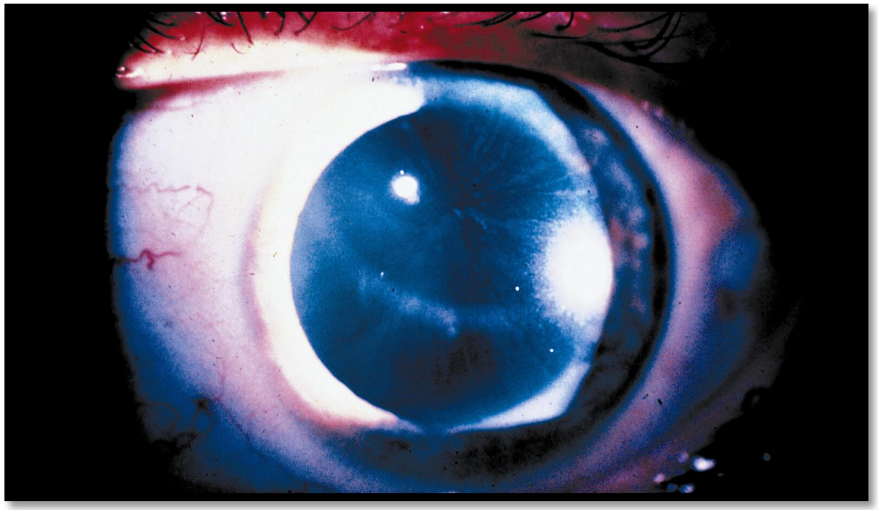


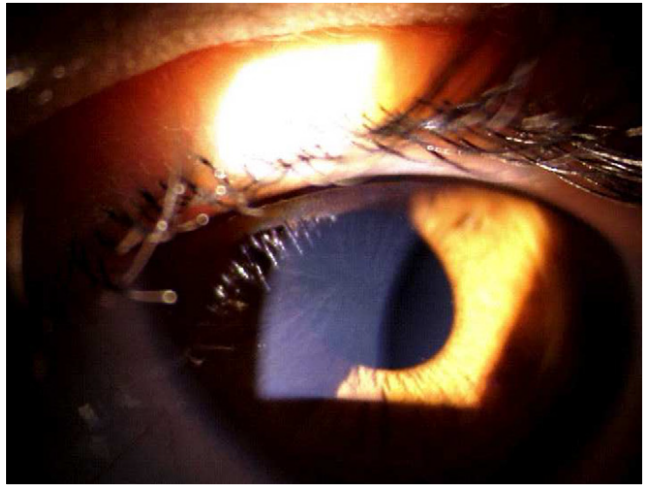
Cornea verticilata

(Fabry)

Chorl-like corneal opacities distributed in a vortex pattern

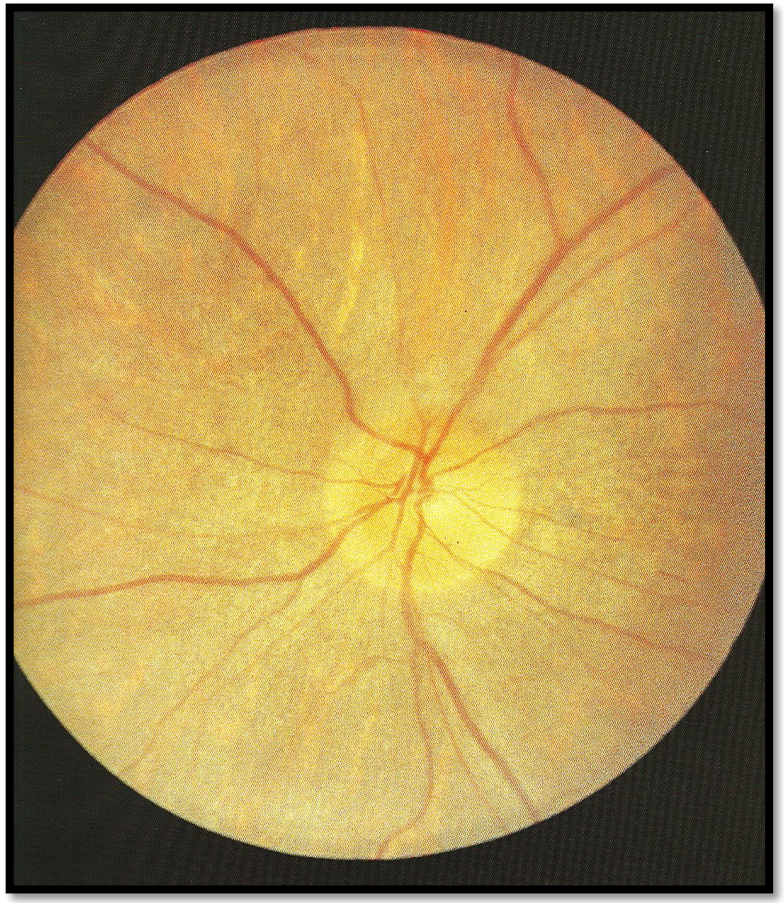






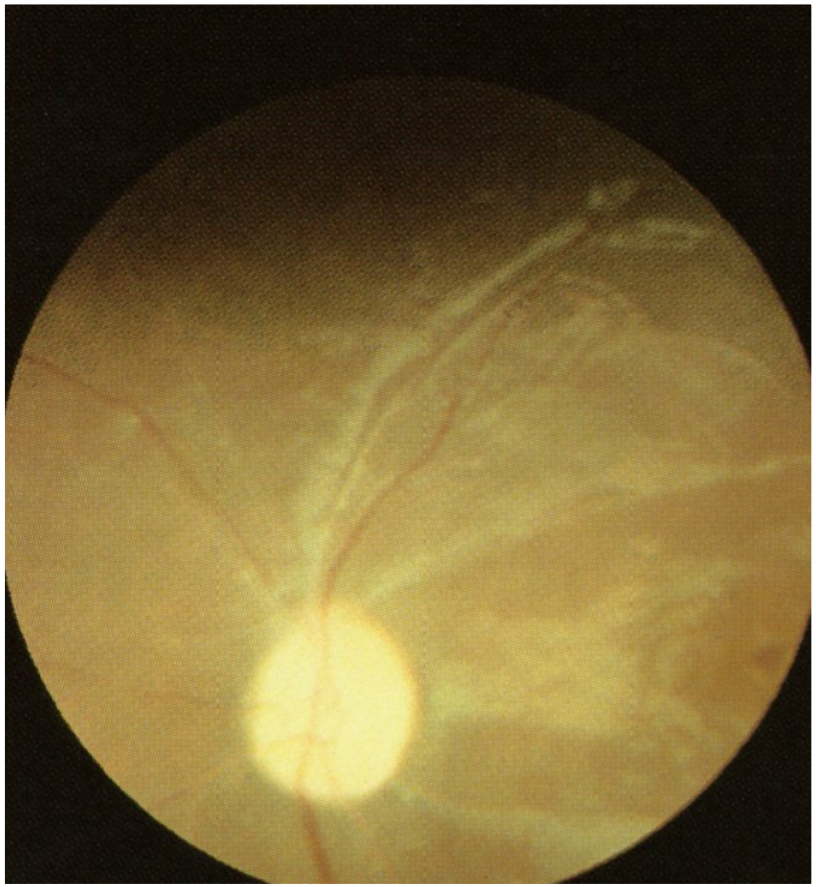
Retinopathy

(MPS II, ML IV, NCLs)



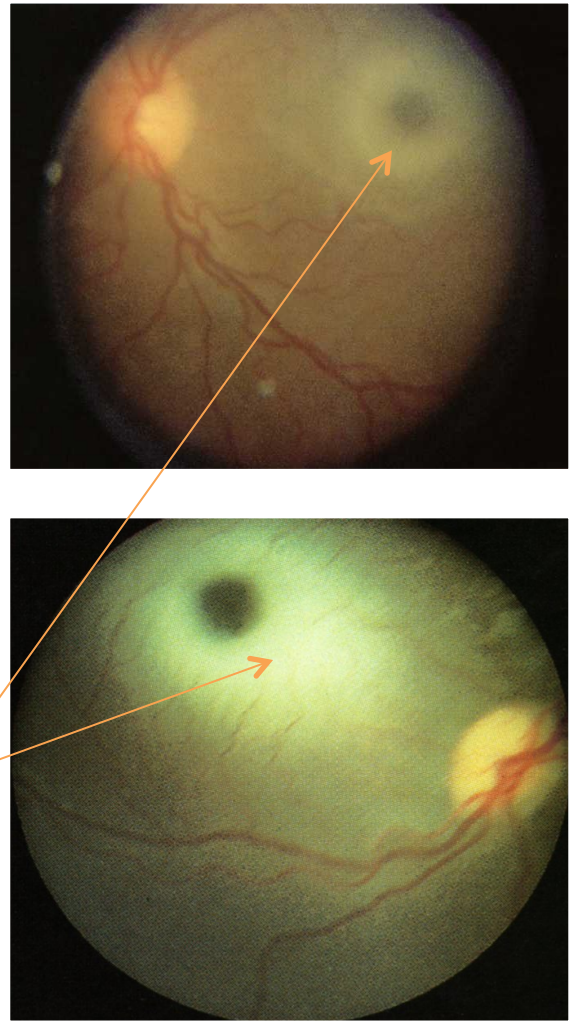
Optic atrophy

(CNL, Krabbe, sialidosis, Schindler)



Cherry red spot

- Farber
- Galactosialidosis
- GM1 & GM2 gangliosidosis
- Metachromatic leukodystropy
- Multiple sulfatase deficiency
- Niemann-Pick disease types A, B, C, D
- Tay-Sachs disease
- Sandhoff disease
- Sialidosis types I & II
- Wolman disease



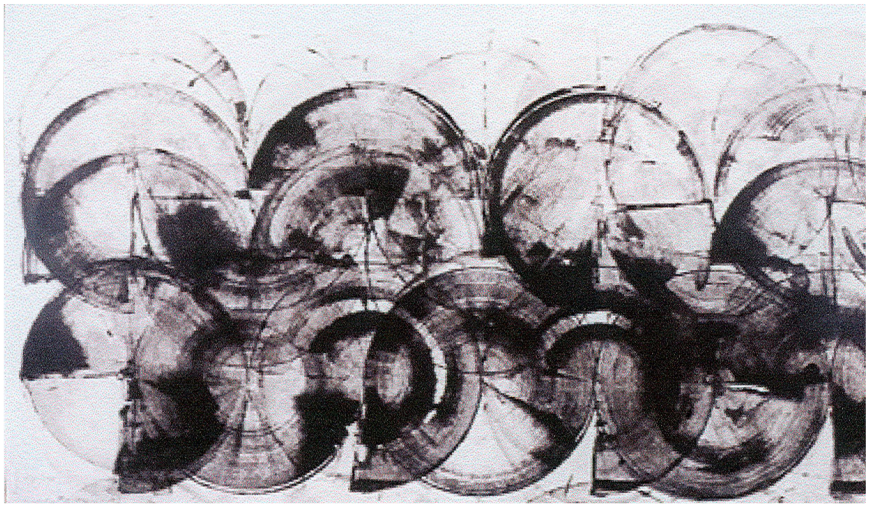
In the center of the pale region lies the foveal pit which lacks ganglion cells (due to heavy deposition of lipid, sphingolipid, or oligosaccharide material), and thus continues to retain its reddish appearance

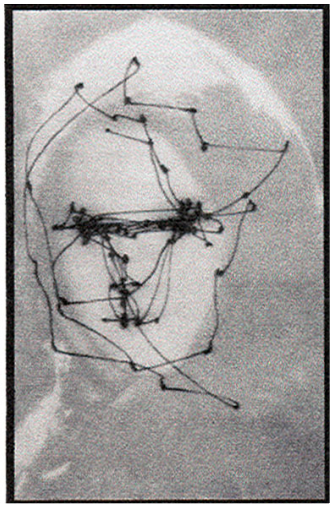
Vertical gaze palsy

(NPC)

Supranuclear opthalmoplegia & abnormal saccades

(GD3, GM2)





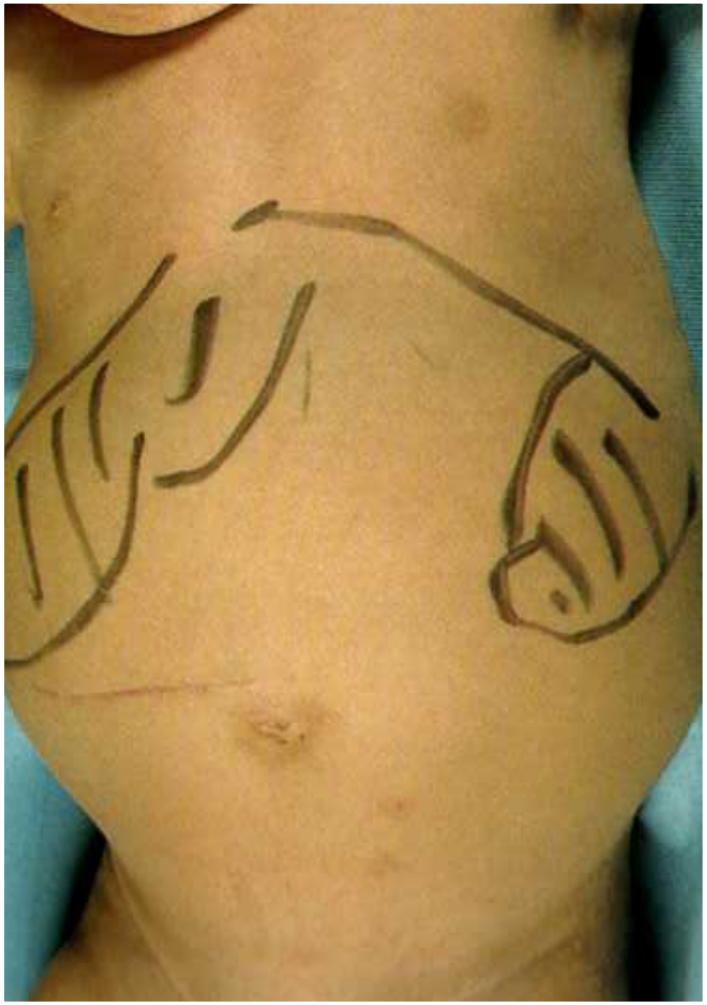
Supranuclear opthalmoplegia & abnormal saccades

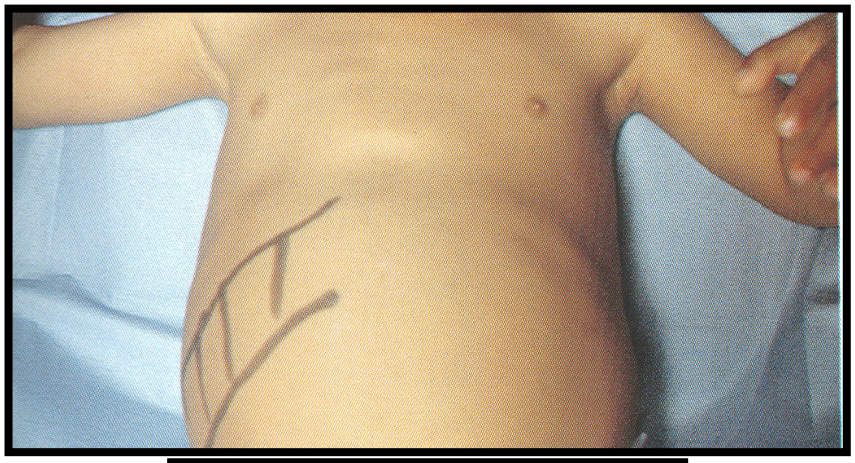
(GD3)

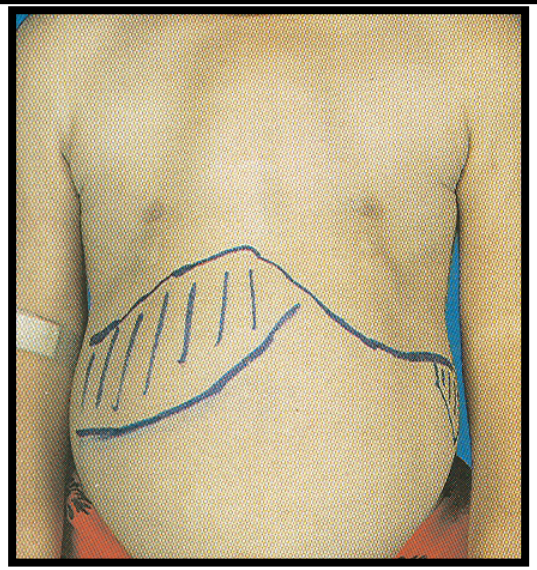
Neurosensory **hearing impairment**

- **Alpha & beta-mannosidosis**
- **MPS**s & **MLs**
- ✓ **GM2** (Tay-Sachs): hyperacousia

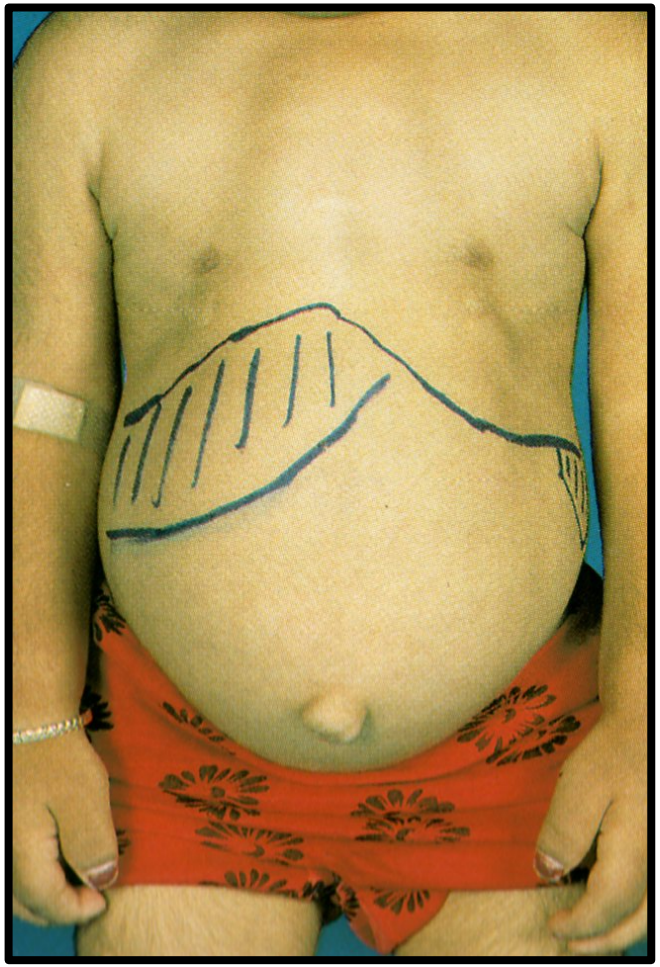
Organomegaly

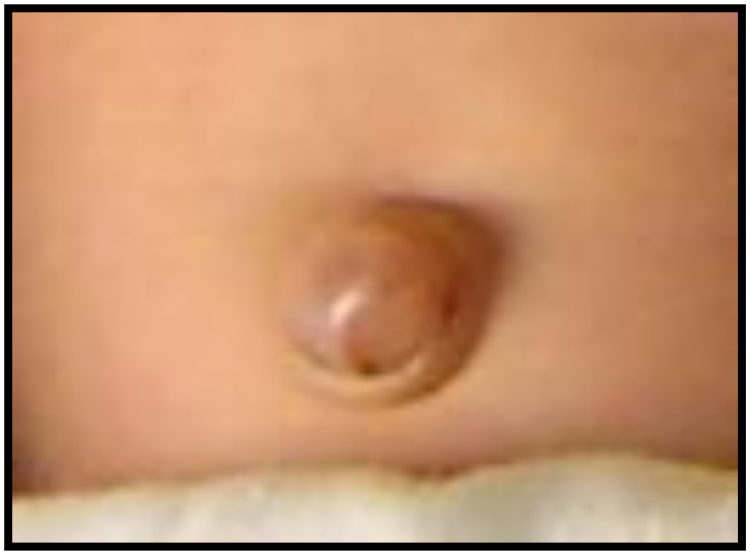




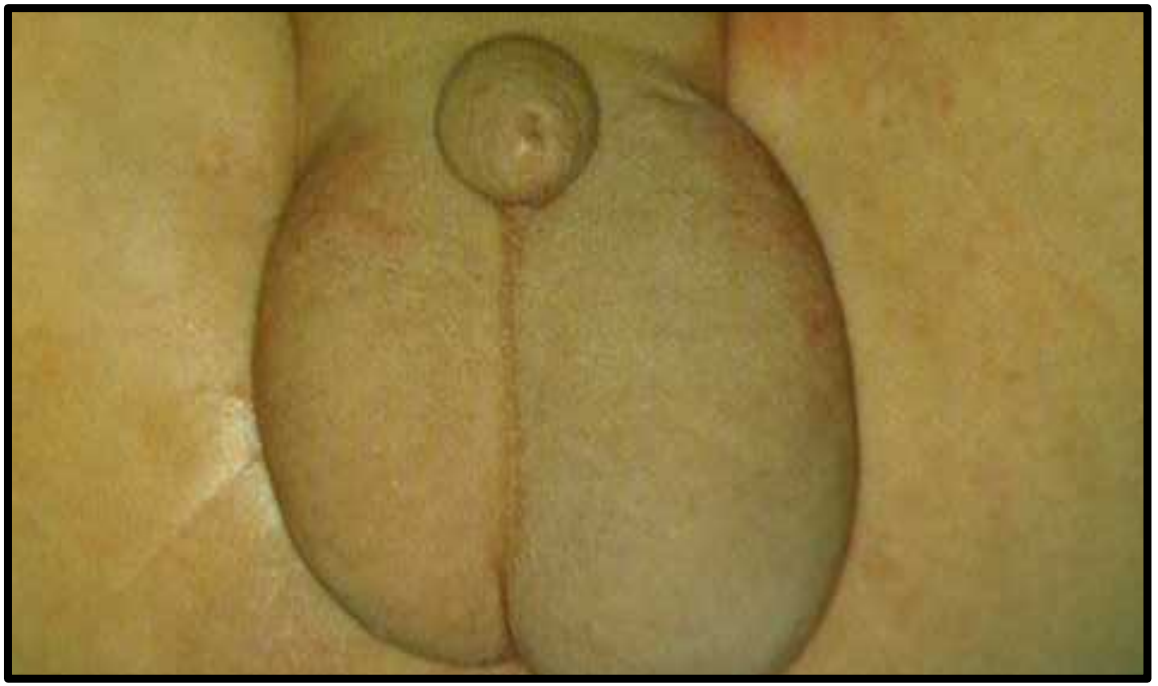


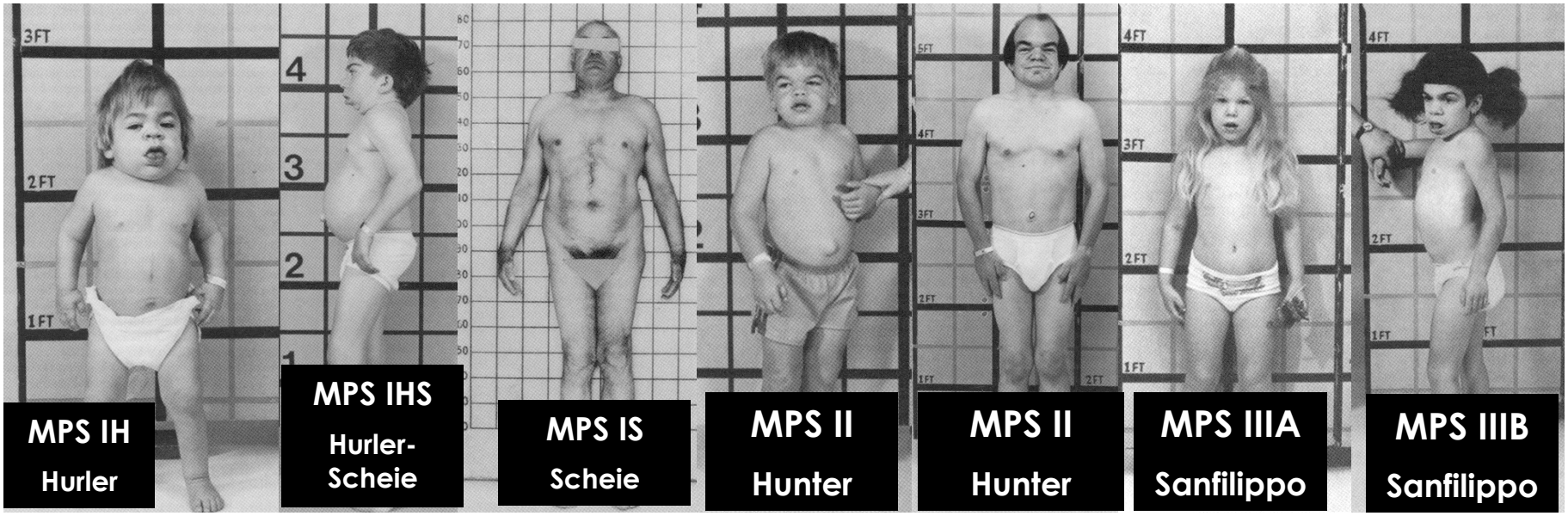
Omphalocele



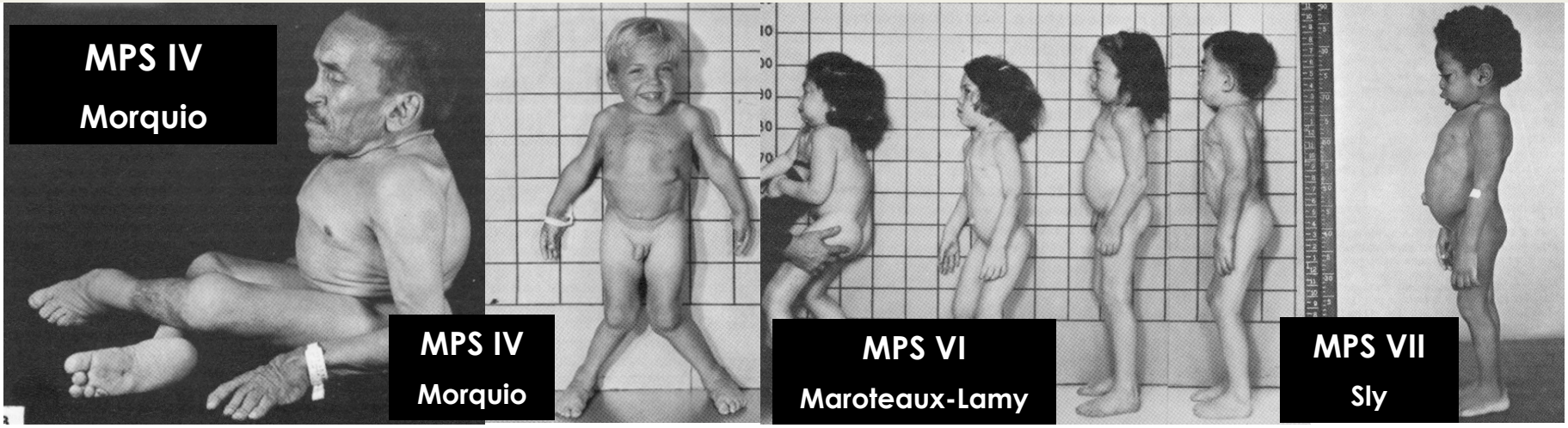


Scrotal oedema





Phenotypic variety: **MPS**s



Progressive coarseness of facial features

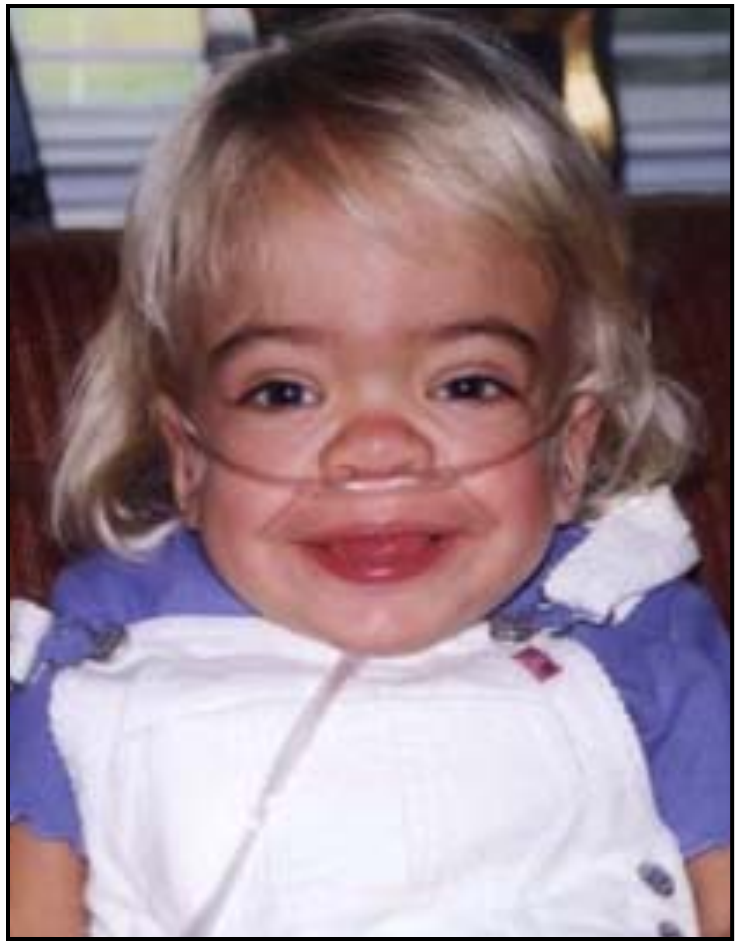
(MPS I)

10 m

12 m

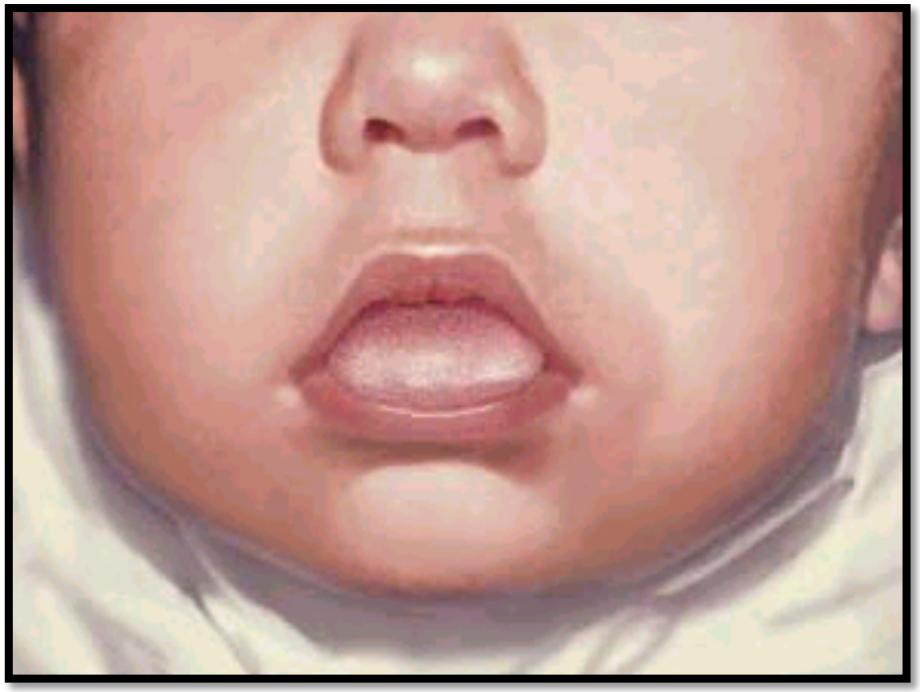
22 m

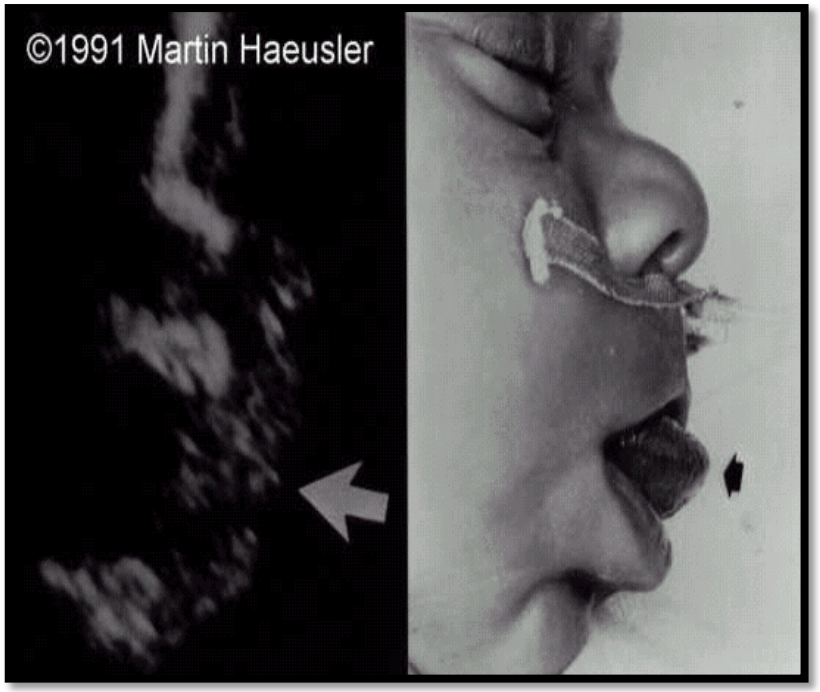
34 m



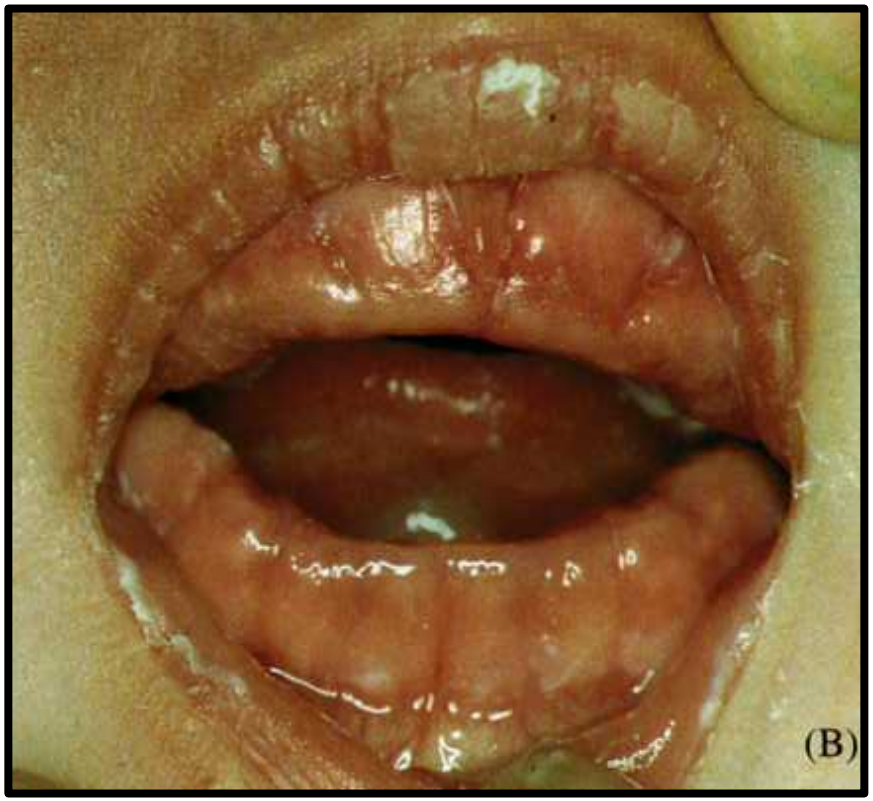
39 m

Macroglossia



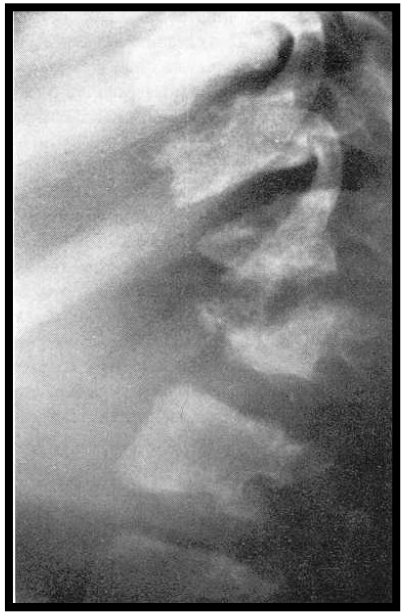


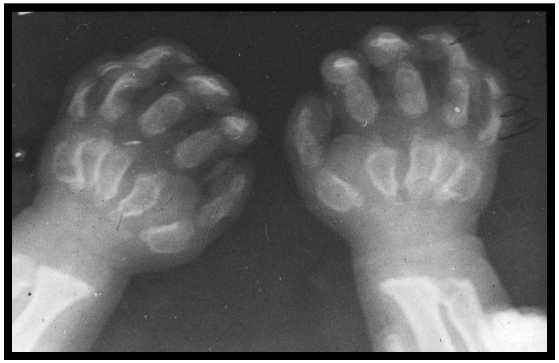
Gum **hyperplasia**

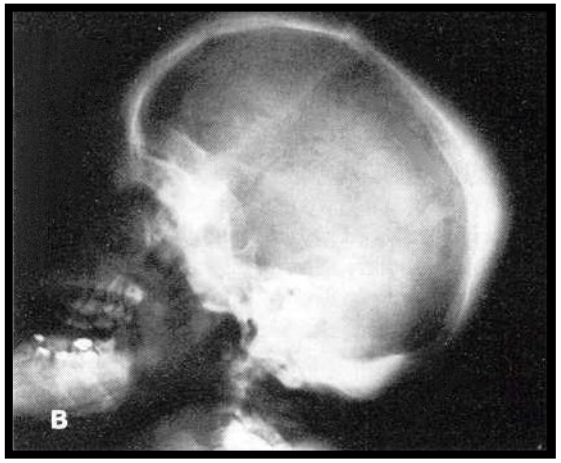


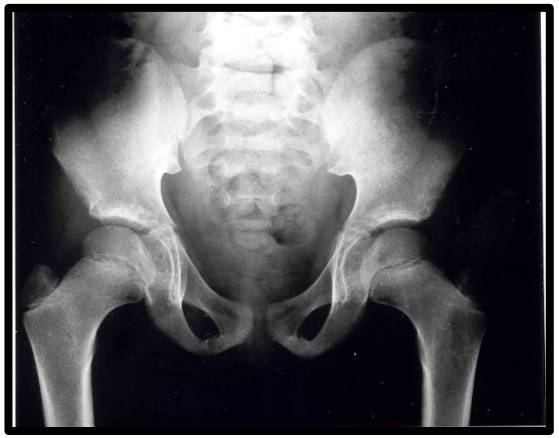
Bone involvement

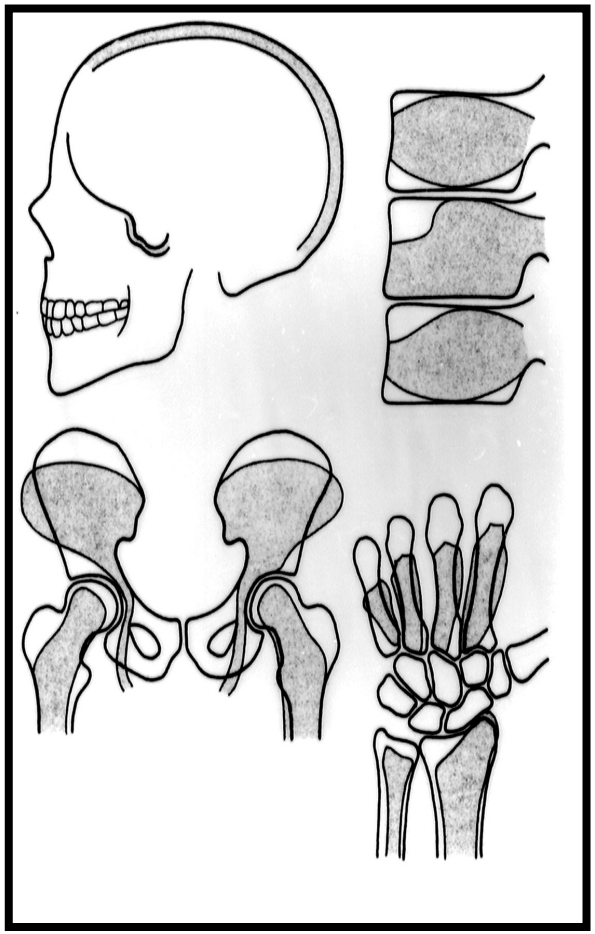
(multiple dysostosis)





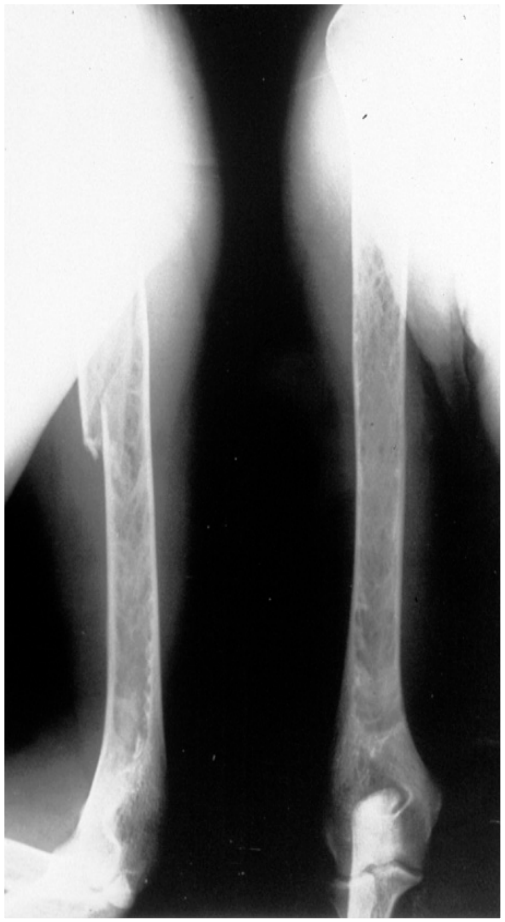


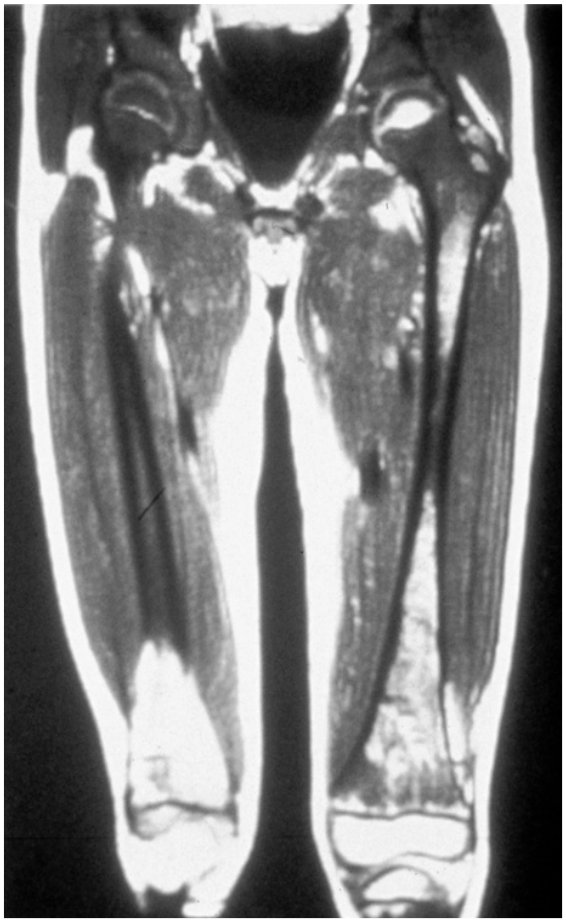


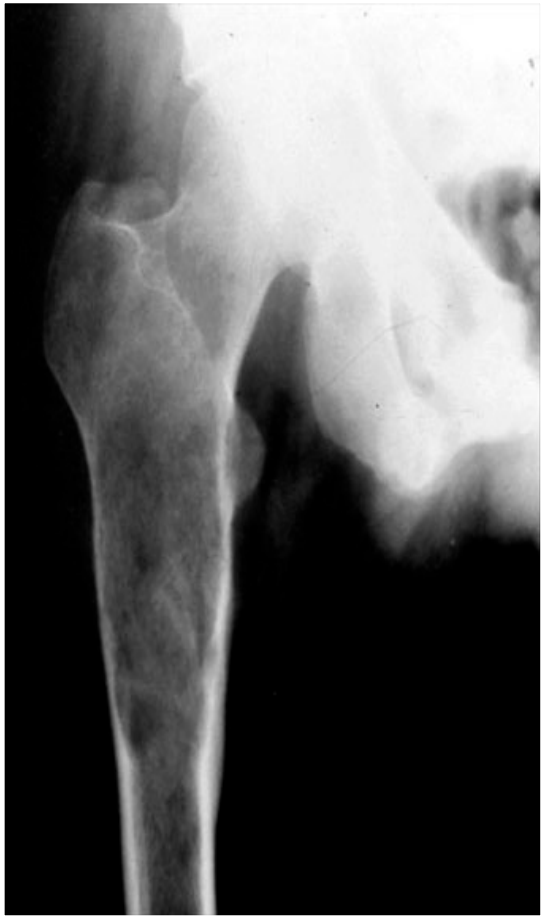


Bone involvement

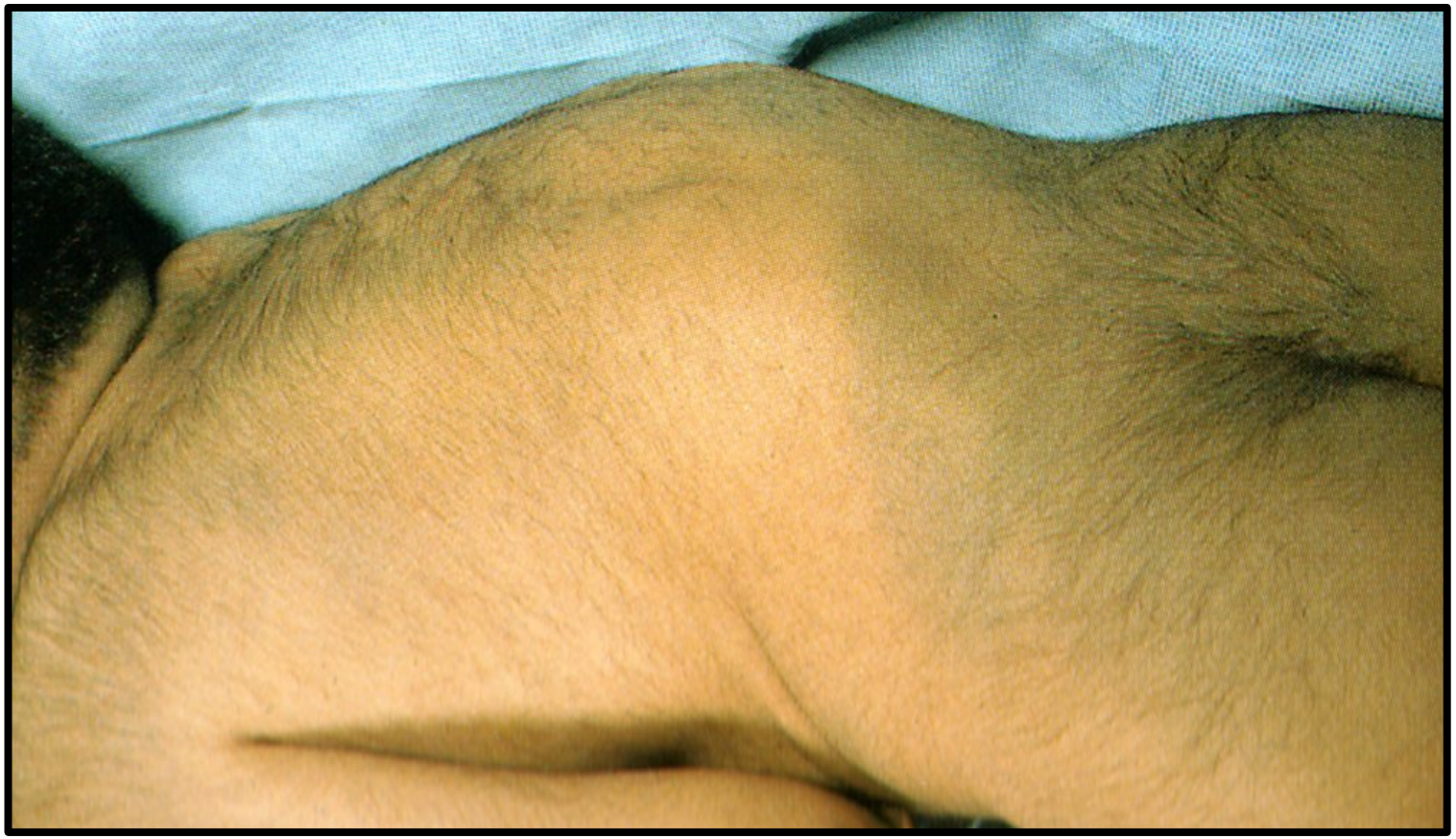
(GD)



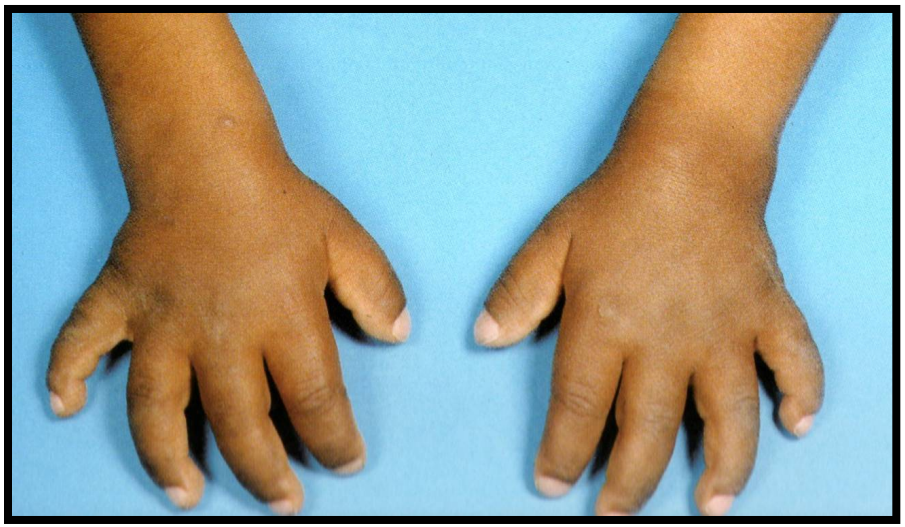


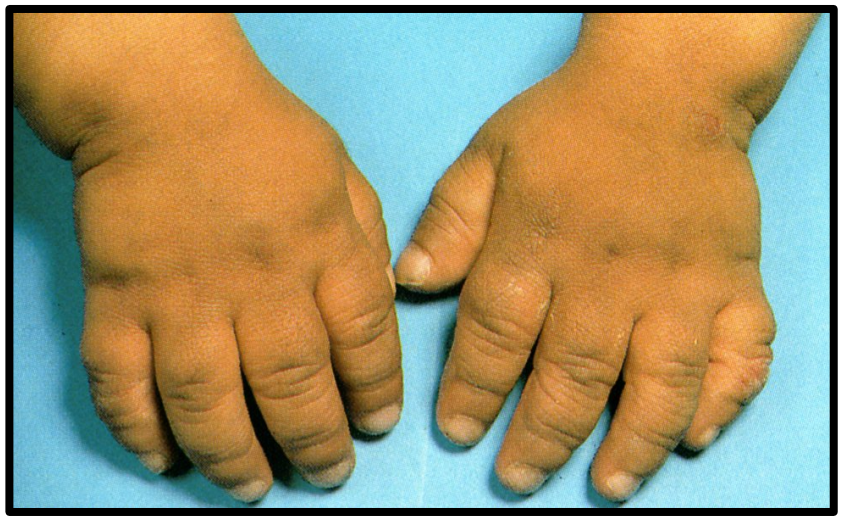


Kyphosis

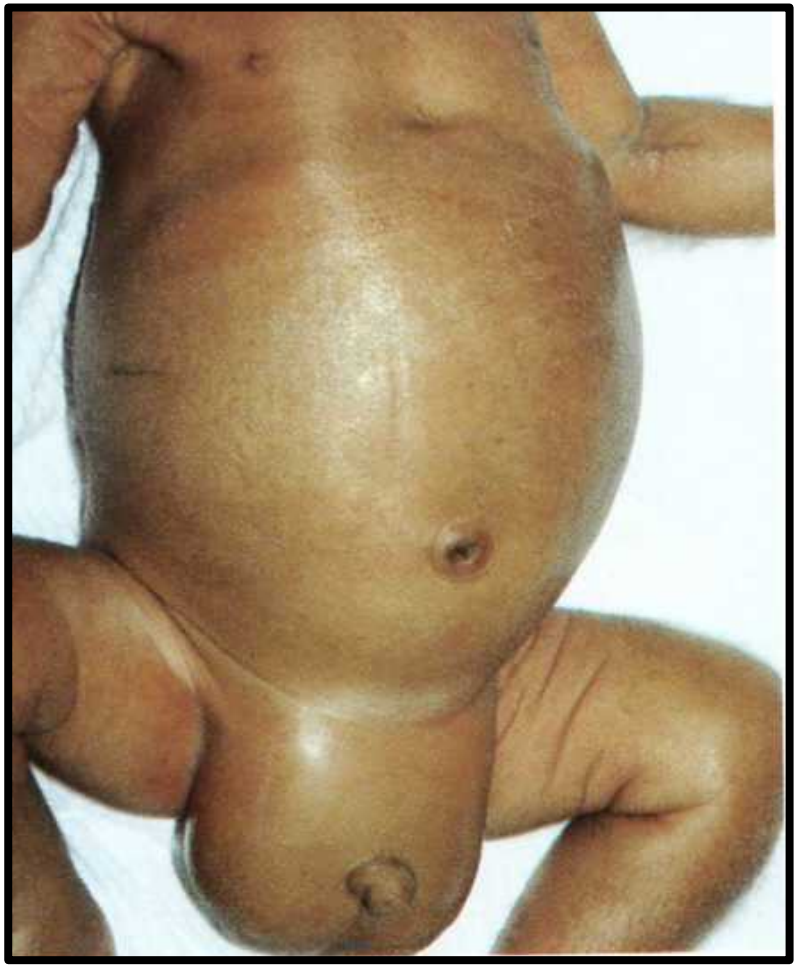


Short & thick **fingers**



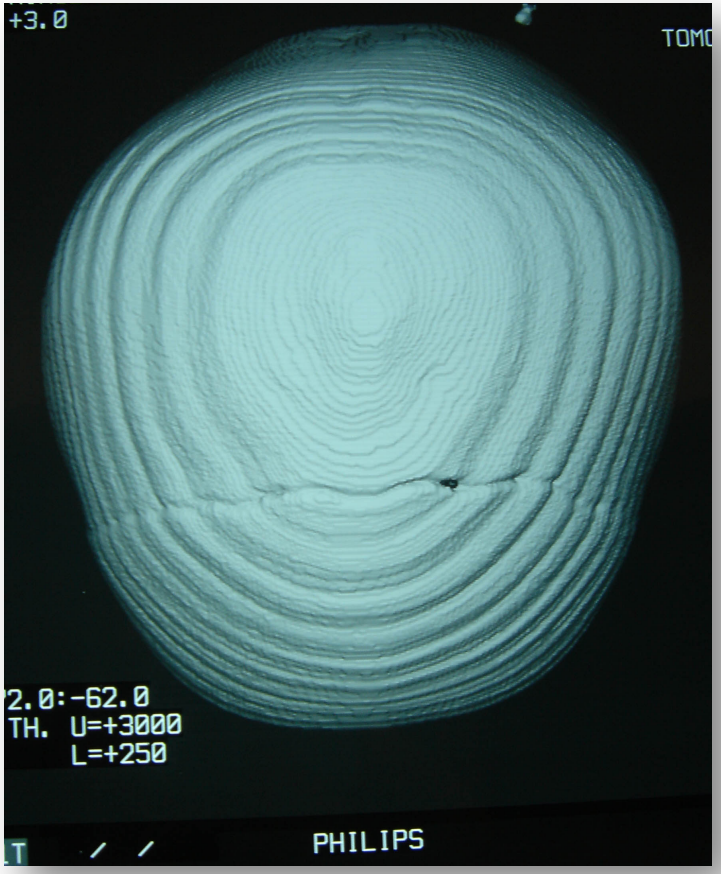


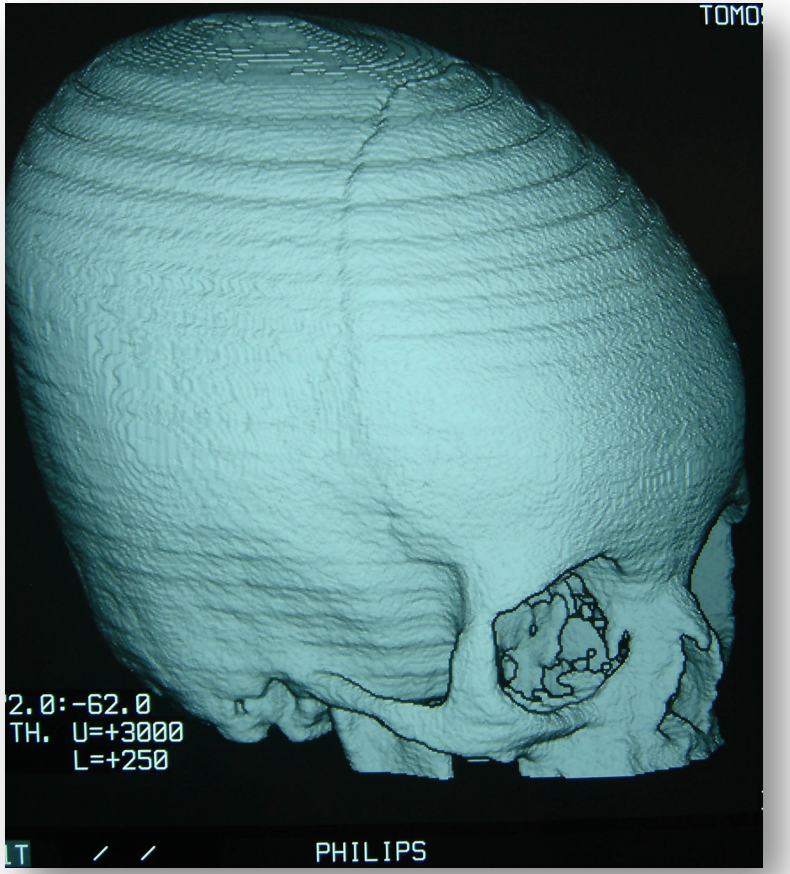
Hydrops fetalis



Craniosynostosis – 3D CT

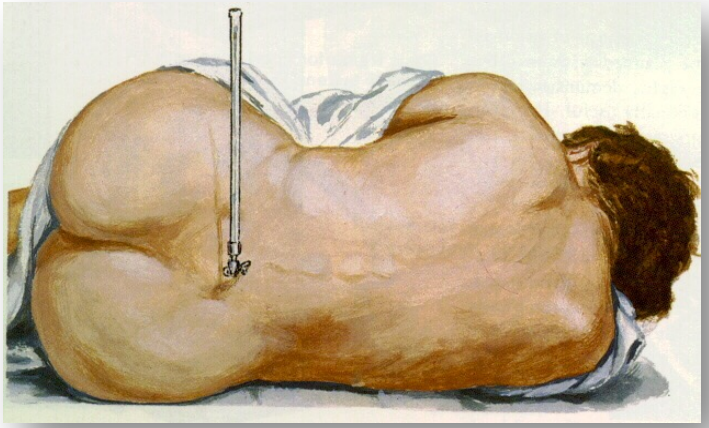
(GD3)

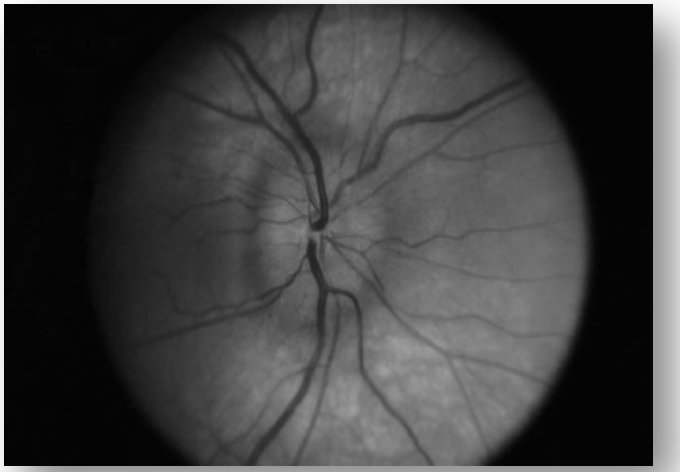


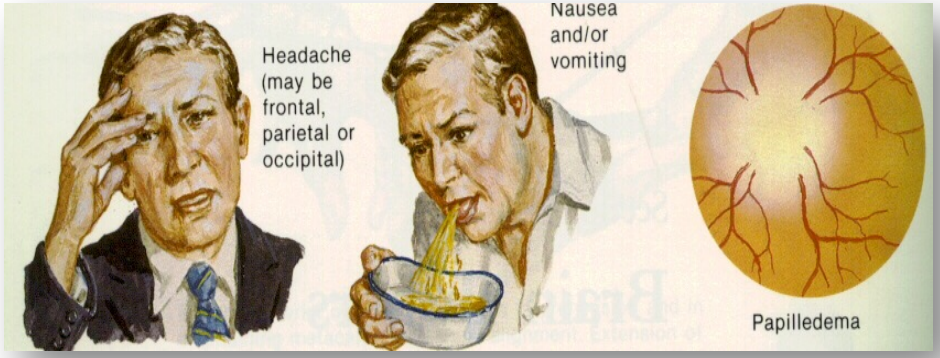


Intracranial **Hypertension**

(MPSs, cystinosis, Pompe)







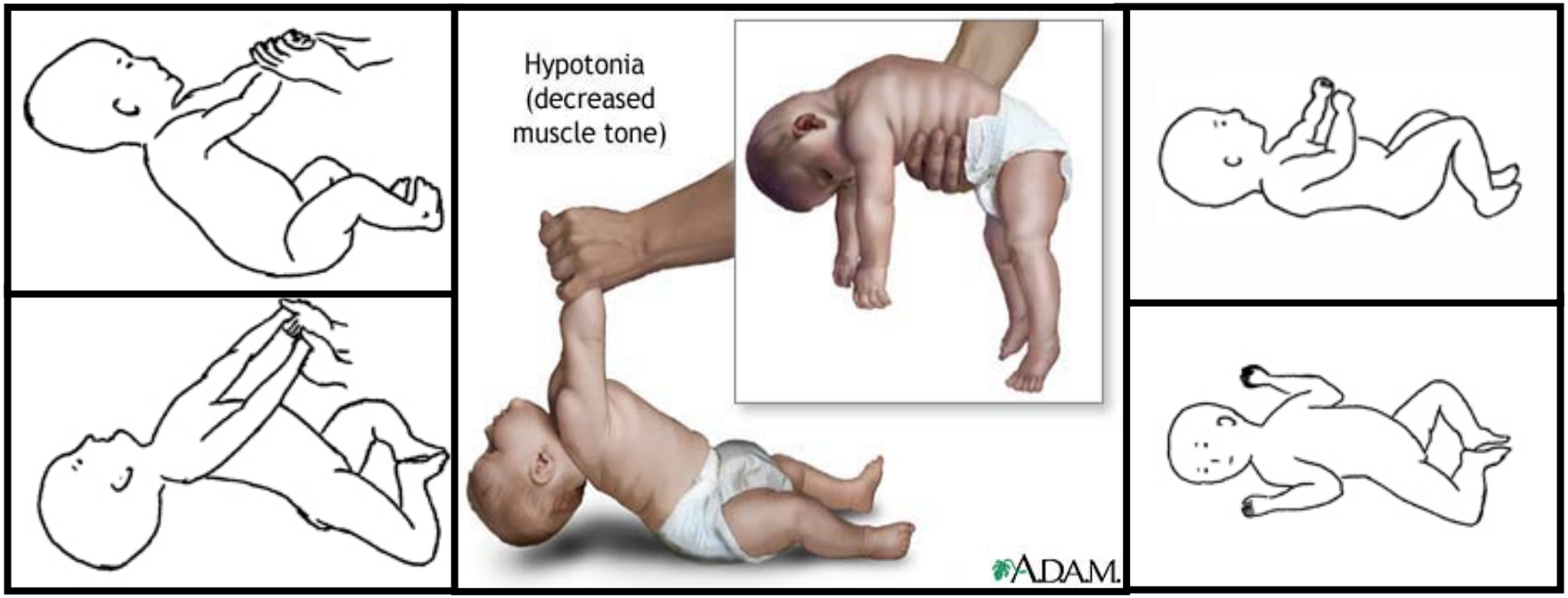
PNS dysfunction

- Muscle hypotonia & weakness *(Pompe)*
- Peripheral neuropathy *(MLD, Krabbe, multiple sulfatase deficiency, Fabry, NPC)*
- Acroparesthesias & pain crises *(Fabry, Krabbe)*

Weakness - hypotonia

Weakness: no movement against gravity - movements only after stimuli

Hypotonia: spontaneous movements & movements against gravity

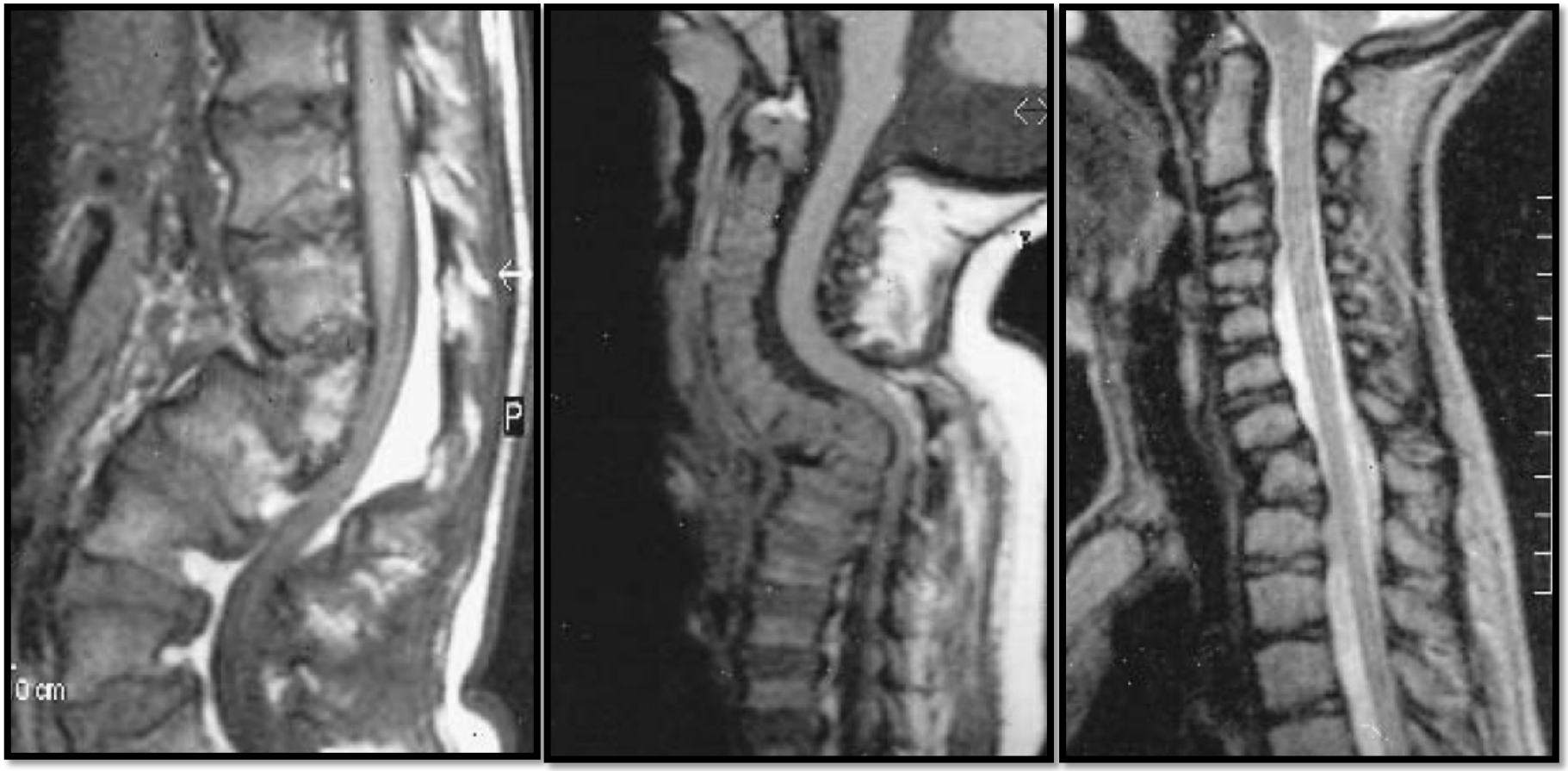


Secondary neurological involvement

- Paraplegia due to spinal cord compressions *(mostly in MPS I, IV, or VI)*
- Carpal tunnel syndrome (almost in all MPSs and MLs)
- Cerebrovascular accidents in Fabry disease *(rarely in MPS II, GD1)*
- Radiculopathy secondary to vertebral compression in osteoporotic patients with GD1

Spinal cord compression due to dysostosis multiplex

(MPS VI)



“Lumpers”: **single disease or group of diseases**

i. Early infantile regression

ii. Eye movement disorders

iii. Extrapyramidal syndrome

iv. Coarse facial features

v. Myoclonus, seizures & optic atrophy

vi. Spasticity & optic atrophy

Group 1: Early infantile neurological regression

- Onset before the first 12–18 months of life
- GM1, GM2, GD2 & 3, ML2, fucosidosis I, Krabbe and NPA
- Usually absent enzyme activities
- Similar neurological and systemic manifestations

Sphingolipidoses

- The three main sphingolipids are:

  ceramide, **sphingomyelin** and the **glycosphingolipids** (including cerebrosides and gangliosides)

- Defects in degradation of these macromolecules produce the LSDs collectively called sphingolipidoses

Sphingolipidoses

- ✓ Since these lipids are synthesized in neural tissue, the storage produced by an SL most frequently affects the **central and peripheral nervous** systems

Additional clues for some sphingolipidoses (i.e. GM1)

- **Cherry red spot**
- **Extraneurological features**
  - dysplastic vertebra
  - signs of storage
    (e.g., macroglossia, hepatomegaly)

Group 2: Eye movement disorders

- NPC
- Late-onset GM2 type B
- GD 3

Group 3: Extrapyramidal syndrome

- Adult GM1
- NPB

Group 3: Coarse facial features

- Most MPSs
- a- & b-mannosidosis
- Galactosialidosis
- MSD
- Fucosidosis 2
- Sialidosis II
- Mucolipidosis II
- GM1

MPSs

- **Profound mental deterioration**
  - MPS 1H (Hurler syndrome)
  - severe form of MPS II (Hunter syndrome)
  - all subtypes of MPS III (Sanfilippo syndrome)

- **Severe behavioral disturbances**, such as hyperactivity, obstinacy and aggression

Mucolipidoses

- Combination of symptoms of **mucopolysaccharidoses** and **sphingolipidoses**
- Striking variation between phenotypes

Group 5: Myoclonus, seizures & optic atrophy

- NCLs
- Sialidosis I
- Aspartoglucosaminouria *(Salla disease)*
- Schindler disease

NCLs

- A group of at least ten genetically distinct disorders
- Intralysosomal aggregation of autofluorescent ceroid and lipofuscin
- NCLs probably constitute the most common group of **progressive encephalopathy** in children

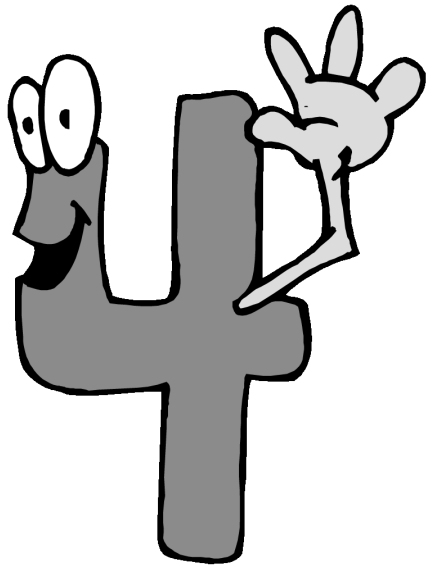
Oligosaccharidoses

- alpha- and beta-mannosidosis
- Fucosidosis
- Schindler disease
- Aspartylglucosaminuria
- Sialidosis *(cherry-red-spot myoclonus syndrome)*

Group 6: Spasticity & optic atrophy

- KD and MLD ➔very well known leukodystrophies
- Long tracts
- Peripheral neuropathy
- Optic atrophy and retinopathy

Peroxisomal disorders



Peroxisomal disorders

Classification of peroxisomal disorders with nervous system involvement.

Disorder	Abbreviation	Gene symbol	Enzyme deficiency	Associated phenotypes
Disorders of peroxisome biogenesis				
–Zellweger spectrum disorders	ZSD, PBD,	Multiple *PEX* genes	Generalized	Zellweger spectrum
–Zellweger syndrome	ZS			
–Neonatal adrenoleukodystrophy	NALD			
–Infantile Refsum disease	IRD			
Rhizomelic chondrodysplasia punctata type 1	RCDP1	*PEX7*	DHAPAT Alkyl-DHAP synthase Phytanoyl CoA hydroxylase	RCDP and variants
Single peroxisomal enzyme/protein deficiencies				
X-linked adrenoleukodystrophy and adrenomyeloneuropathy	XALD AMN	*ABCD1*	ABC transporter protein	XALD, XAMN, and variants
Peroxisomal acyl-CoA oxidase 1 deficiency	ACOX1D		Peroxisomal acyl-CoA oxidase 1	NALD-like disease
D-bifunctional protein deficiency	DBPD	*HSD17B4*	D-bifunctional protein	ZS-like disease
Rhizomelic chondrodysplasia punctata type 2	RCDP2	*GNPAT*	Dihydroxyacetone phosphate acyltransferase	RCDP and variants
Rhizomelic chondrodysplasia punctata type 3	RCDP3	*AGPS*	Alkyl-DHAP synthase	RCDP and variants
Refsum disease	RD	*PHYH*	Phytanoyl-CoA hydroxylase	Refsum disease
2-Methylacyl-CoA racemase deficiency	AMACRD	*AMACR*	AMACR	Adult-onset polyneuropathy

Zellweger spectrum disorders
(peroxisomal biogenesis)

Neonatal profile

- Severe muscular hypotonia with resultant poor feeding
- Seizures
- Hepatic dysfunction incl. mixed hyperbilirubinemic jaundice
- Dysmorphic signs

Zellweger spectrum disorders
(peroxisomal biogenesis)

Childhood profile

- Retinopathy often leading to early blindness
- Sensorineural deafness
- Hepatic dysfunction that may involve symptoms of vitamin K-responsive coagulopathy
- Developmental delay
- Failure to thrive
- Dysmorphic signs
- Adrenal insufficiency

Zellweger spectrum disorders
(peroxisomal biogenesis)

Late-onset mild profile

- Cerebellar ataxia
- Neuropathy
- Sensorineural deafness
- Retinopathy
- Cholestatic liver disease during infancy

Bony changes in the neonatal and childhood group

- Large fontanel
- Osteopenia of long bones
- In 50%, calcified stippling in the epiphyseal and periarticular regions of large joints, especially the patellar region

Cerebral changes in the neonatal and childhood group

- Neocortical dysgenesis, due to neuronal migration failure
- Metabolic changes involving the process of myelination, and in some cases leading to later demyelination

X-linked ALD

(single peroxisomal protein deficiency - peroxisomal beta oxidation)

- Addison's disease in boys, adolescents and adults
- Insidious onset with hyperactive behavior & declining school performance
- Central deafness
- Decreased visual acuity
- Spastic tetraparesis
- Cognitive decline
- Seizures

Leading to a severe disability and death within years after onset of symptoms

RCDP

- Symmetric proximal shortening of the extremities (rhizomelia)
- Severe contractures from birth
- Typical facial appearance
- Cataracts (from birth or in the first months of life)
- Severe growth retardation
- Developmental delay

Other types - **Refsum disease**

- Early-onset retinitis pigmentosa
- Cerebellar ataxia
- Polyneuropathy
- Less constant features:
  - sensorineural hearing loss
  - anosmia
  - ichthyosis
  - skeletal malformations
  - cardiac abnormalities

Congenital disorders of glycosylation

CDGs

- > 50 disorders due to congenital defects in N-linked glycosylation
- clinical syndromes affecting multiple systems including:
  - CNS
  - muscle function
  - immunity
  - endocrine system
  - coagulation
- Some: unexpectedly long-term survival
- Some: Non-syndromic intellectual disability

PMM2-CDG

- Abnormal fat pads
- Inverted nipples
- Arachnodactyly
- Mild muscle hypotonia
- Strabismus at birth
- However
  - abnormal fat distribution might disappear with older age
  - milder cases frequently present without any of these dysmorphic features
  - Endocrine disturbance and thrombotic complications
  - severe communication problems vs. cheerful habitus
  - Many patients survive to adulthood, losing the syndromal aspects

PMI-CDG

- Hepatointestinal phenotype
- Chronic diarrhea (protein-losing enteropathy)
- Coagulation defects
- Liver disease
- No dysmorphic features
- Normal development
- Liver fibrosis in childhood or in young adulthood

Other subtypes

- Oculocerebellar syndrome with occasional ichthyosis
- Dilated cardiomyopathy
- Syndromal dystroglycanopathies
- Severe early symptoms including eye malformations, muscle weakness, and developmental delay
- Mild congenital myasthenia leading to muscle weakness
- Severe hearing loss & skeletal abnormalities
- Microcephaly, ventricular septal defect, failure to thrive, hyperthermia, ↑CK

Other subtypes

- Distal limb malformations
- Skeletal dysplasia
- Cerebrocostomandibular syndrome
- Short stature & cutis laxa
- Radioulnar synostosis
- Conotruncal malformation

Dystroglycanopathies

Alpha-dystroglycanopathies

- Syndromes of variable severity imitating muscle-eye-brain disease
- Severe neurologic disease with developmental delay and muscle weakness with CK elevations
- Mild limb-girdle-type muscle dystrophy with cardiomyopathy
- alpha dystroglycanopathy with high CK levels, abnormal muscle histology, and associations with microcephaly and severe seizure disorder

Genetic and Metabolic Disorders to Consider as **Differential Diagnoses in CDGs**

Genetic Disorders	Metabolic Disorders
Prader-Willi syndrome	Mitochondrial disorders
Congenital muscular dystrophies • Muscle-eye-brain disease • Fukuyama congenital muscular dystrophy • Walker-Warburg syndrome	Peroxisome biogenesis disorders • Zellweger syndrome spectrum
Congenital myopathies	Urea cycle defects

Smith-Lemli-Opitz syndrome

- Congenital multiple anomaly/intellectual disability syndrome
- Deficiency of cholesterol synthesis resulting from a deficiency of 7-dehydrocholesterol (7DHC) reductase encoded by DHCR7
- Autosomal recessive pattern of inheritance

Smith-Lemli-Opitz syndrome

- Prenatal and postnatal growth retardation
- Microcephaly
- Variable degree of intellectual disability
- Multiple major and minor malformations

Smith-Lemli-Opitz syndrome

- Distinctive facial features
- Cleft palate
- Postaxial polydactyly
- Syndactyly of the toes (2nd & 3rd finger)
- Underdeveloped external genitalia in males

GLUT-1 deficiency

- Infantile seizures refractory to anticonvulsants
- Microcephaly
- Delays in mental and motor development
- Spasticity
- Ataxia
- Dysarthria
- Other paroxysmal neurologic phenomena, often occurring prior to meals

GLUT-1 deficiency

- Affected infants normal at birth
- Uneventful pregnancy and delivery
- Seizures usually begin between 1 & 4 months
- Preceded by apneic episodes or abnormal eye movements
- Atypical presentations
    - mental retardation
    - intermittent ataxia without seizures
    - movement disorders (choreoathetosis & dystonia)

DD only!

- No history
- No regression
- Rest of the examination normal

DD only!

- Propionic/methylmalonic acidemia
- D-2 or L-2 hydroxyglutaric aciduria
- UCDs
- Homocystinuria
- Phenylketonuria (missed by neonatal screening)
- Creatine deciciency
- MPSIII (mainly A or C)

DD without a clue

- **Importance of re-evaluation!!!**
- **Diagnoses increase 5-20% with return visits**
  - Two visits in the 1st year of life
  - Yearly until school
  - Re-evaluation during puberty

When to think about IME?

- Consider IME in parallel with other more common conditions
- Be aware of symptoms that persist and remain unexplained after initial treatment
- Don’t confuse a symptom or a syndrome with etiology
- IME can present at any age from fetal life to old age

When to think about IME?

- Although most IME are autosomal recessive disorders, the majority of cases appear sporadic
- Take care first of the patient (emergency treatment), and then of the family (genetic counselling)
- Initially consider IME amenable to treatment

DON'T MISS A TREATABLE DISORDER!!!

The importance of making a diagnosis

- Parental knowledge/acceptance
- Prognosis
- Recurrence risk to patients and siblings
- Option of prenatal diagnosis and genetic counselling in subsequent pregnancies
- **There may be a treatment**

Questions?

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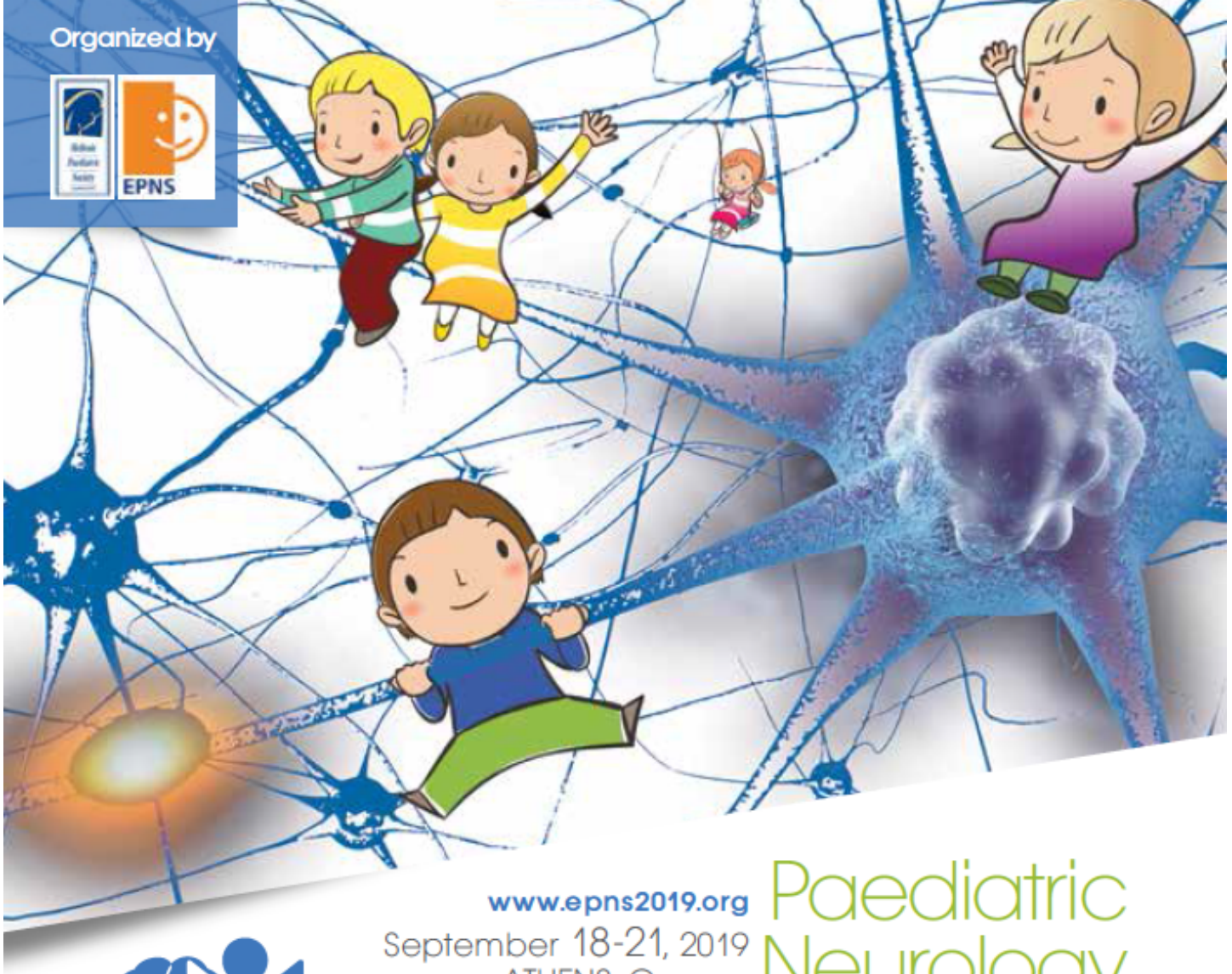

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Thank you very much for your attention!