Signs and Symptoms in Metabolic Diseases

Dr. Engin KÖSE

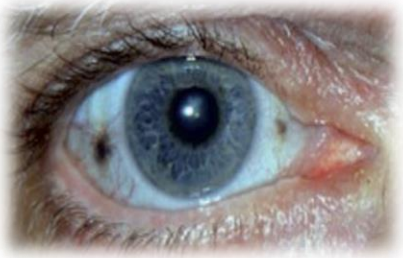
Ankara University Faculty of Medicine

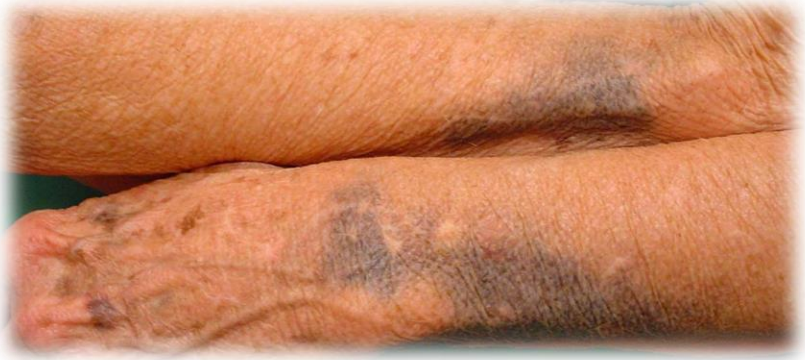
Pediatric Metabolism

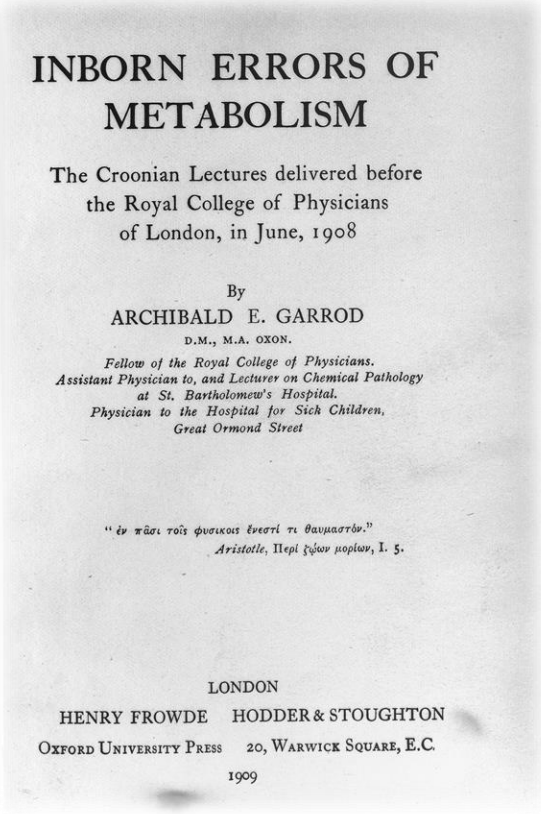
Inborn Errors of Metabolism


Sir Archibald Garrod,

- Archibald Garrod
- 1908
- Anormal biochemical reaction
- Autosomal recessive inheritance







INBORN ERRORS OF METABOLISM

The Croonian Lectures delivered before the Royal College of Physicians of London, in June, 1908

By

ARCHIBALD E. GARROD

D.M., M.A. OXON.

Fellow of the Royal College of Physicians.
Assistant Physician to, and Lecturer on Chemical Pathology at St. Bartholomew's Hospital.
Physician to the Hospital for Sick Children, Great Ormond Street

"ἐν πᾶσι τοῖς φυσικοῖς ἔνεστί τι θαυμαστόν."
Aristotle, Περὶ ζῴων μορίων, I. 5.

LONDON

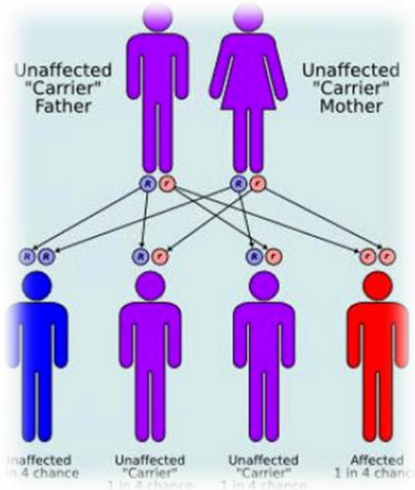
HENRY FROWDE HODDER & STOUGHTON

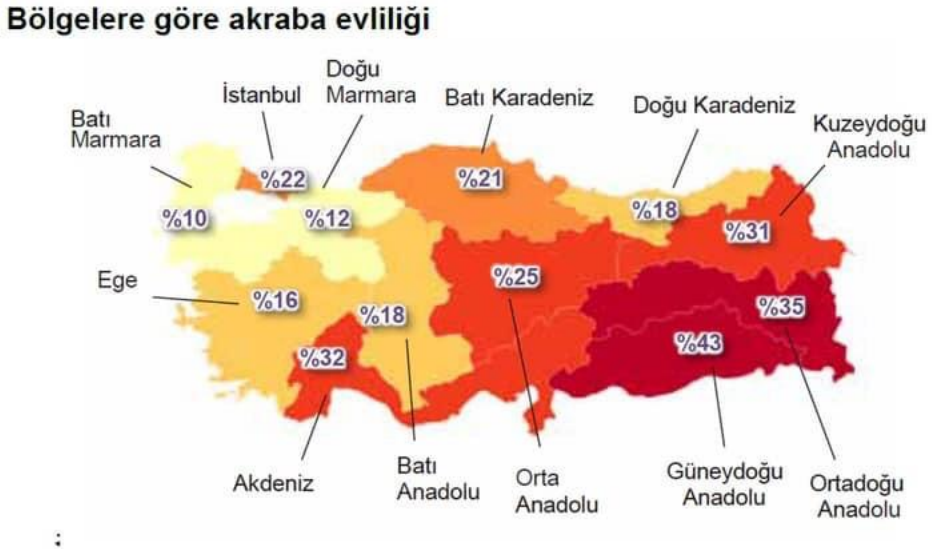
OXFORD UNIVERSITY PRESS 20, WARWICK SQUARE, E.C.

1909

Inborn Errors of Metabolism

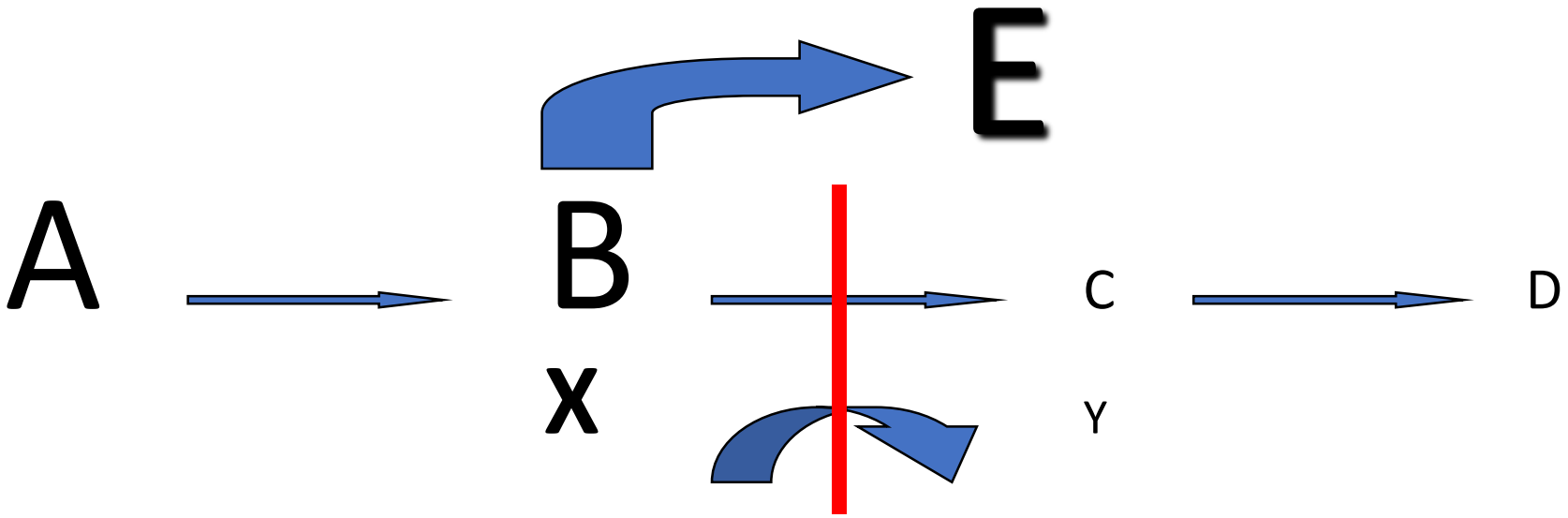
- Rare disease
- But when considered cumulatively, its frequency:
  - 1:4000-5000
  - Consanguineous marriage frequency !!!!!
  - %75 Autosomal recessive inheritance





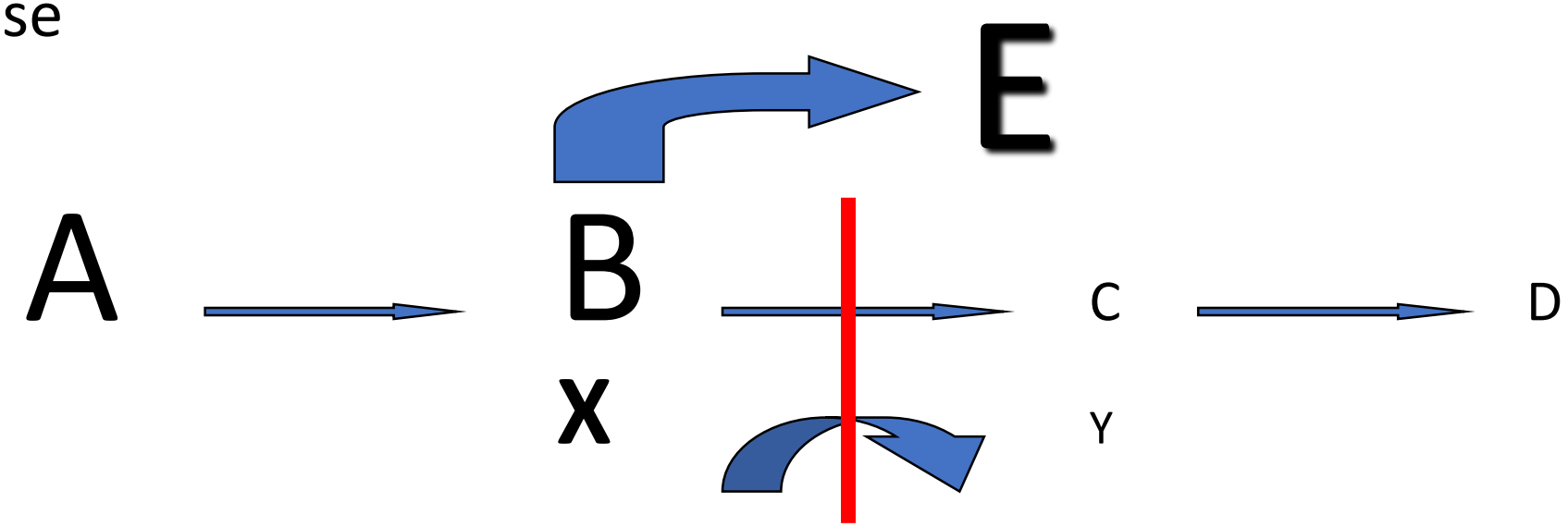
Inborn Errors of Metabolism

- Pathological pictures caused by genetic defects in the enzyme or carrier proteins involved in the synthesis or degradation of proteins, carbohydrates and fatty acids



Inborn Errors of Metabolism

- The required specific end product cannot be produced
- Precursors, indicative of the defective enzyme, accumulate and may show toxic effects
- Activity increases in normal alternating routes, abnormal metabolites increase



Why We Should Know Inborn Errors Of Metabolism?

- Reduce mortality rate
- To prevent irreversible organ damage
- Avoiding long, laborious and expensive diagnostic processes
- Genetic counseling

Why Should We Think Metbolic Disease?

- Metabolic diseases can occur at any age
- History and physical examination!
- Collect and store samples properly prior to emergency treatment.
- Be aware of the important clinical pictures that metabolic diseases should be considered in differential diagnosis.
- * Prioritize and rule out curable metabolic diseases.
- If in doubt, consult your metabolic specialist.

When Should We Think Metabolic Disease?

- Pregnancy history:
  - Mother's health
  - HELLP, AFLP
- Family history:
  - Consanguineous marriage
  - Unexplained death of newborn and infant
  - Similar illness
- Medical history:
  - Recurrent attacks of acidosis, hypoglycemia, acute encephalopathy
  - Intolerance to some foods
  - Self-injurious behavior
  - Psychiatric symptoms
  - Seizure
  - Observation of irritability, convulsion, ataxia in childhood diseases after vaccination
- Type of growth retardation:
  - Mental retardation
  - Loss of acquired skills
  - Hypotonia
  - Speech delay

When Should We Think Metabolic Disease?

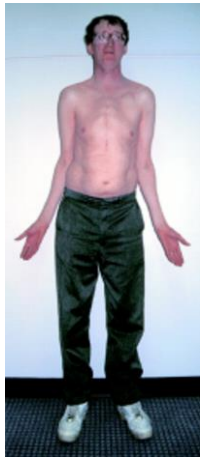
- **<u>Neonatal period:</u>**
  - Feeding difficulties
  - Vomiting
  - Dehydration
  - Sepsis
  - Special odor
  - Breathing difficulty
  - Jaundice
  - Convulsion
  - Hypotonia
  - Lethargy, coma
  - Hydrops fetalis
  - Facial dysmorphism
  - Hepatomegaly
  - Cataract
  - Sudden death

When Should We Think Metabolic Disease?

- **Infancy and childhood:**
  - **Acute and recurrent symptoms:**
    - Recurrent vomiting, lethargy, coma, ataxia
    - Rapid breathing
    - Convulsion
    - Encephalopathy
  - **Chronic progressive general symptoms**
    - Motor and mental retardation, behavioral disorders
    - Hypotonia, hypertonia, opistotonus
    - Specific smell, myopathy
    - Microcephaly, macrocephaly, hydrocephalus
    - Dysmorphic appearance

When Should We Think Metabolic Disease?

- **<u>Symptoms concerning a specific organ:</u>**
  - Cardiomyopathy
  - Dysmorphic appearance
  - <u>Lens findings, retinal disorders, cataracts</u>
  - Organomegaly
  - Unexplained liver disease
  - Renal symptoms
  - Changes in hair, nails and skin
  - Skeletal changes



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

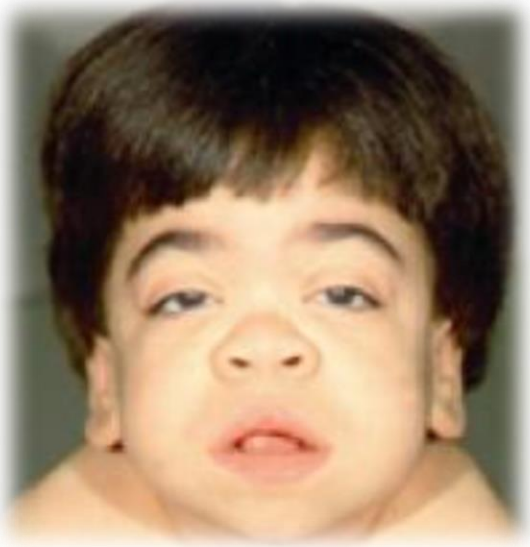
Homocytinuria (downward dislocation= low IQ),

Marfan syndrome, upward (upward= normal IQ)

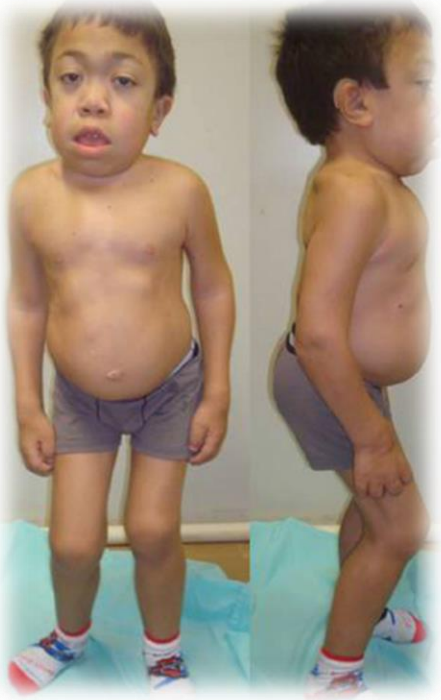
When Should We Think Metabolic Disease?

- Dysmorphic appearance:

I cell



MPS I



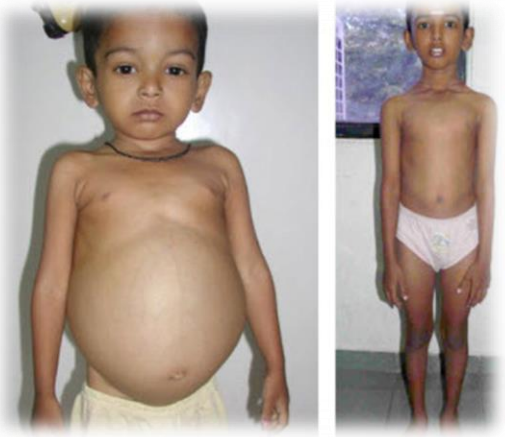
MPS VI

MPS IV

When Should We Think Metabolic Disease?

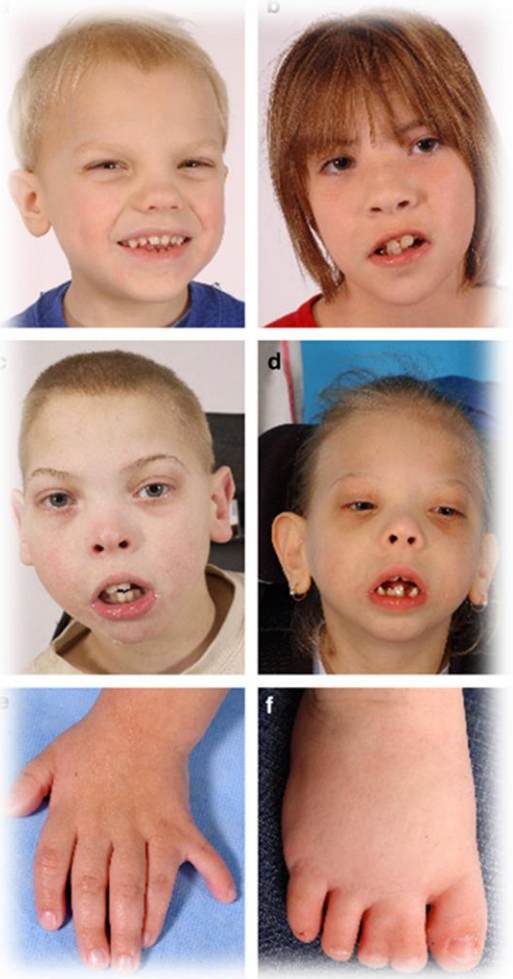
- Dysmorphic appearance:

Zellweger sendromu

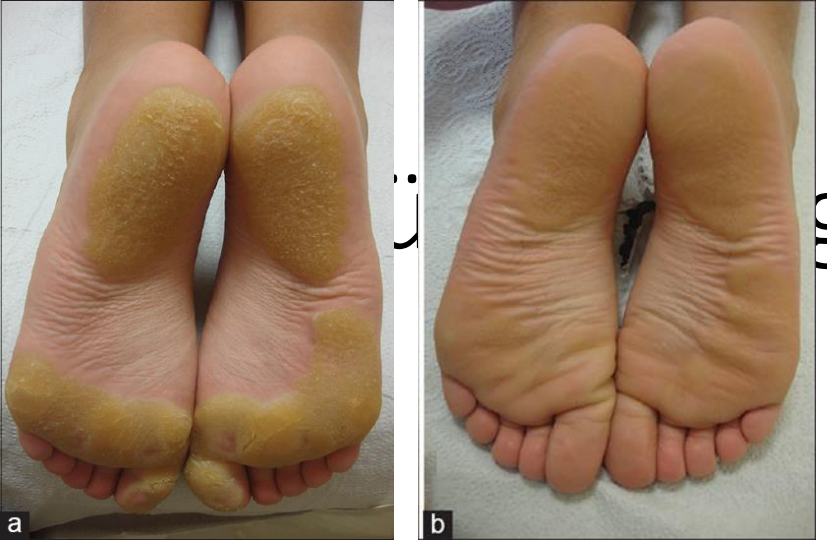


Gaucher

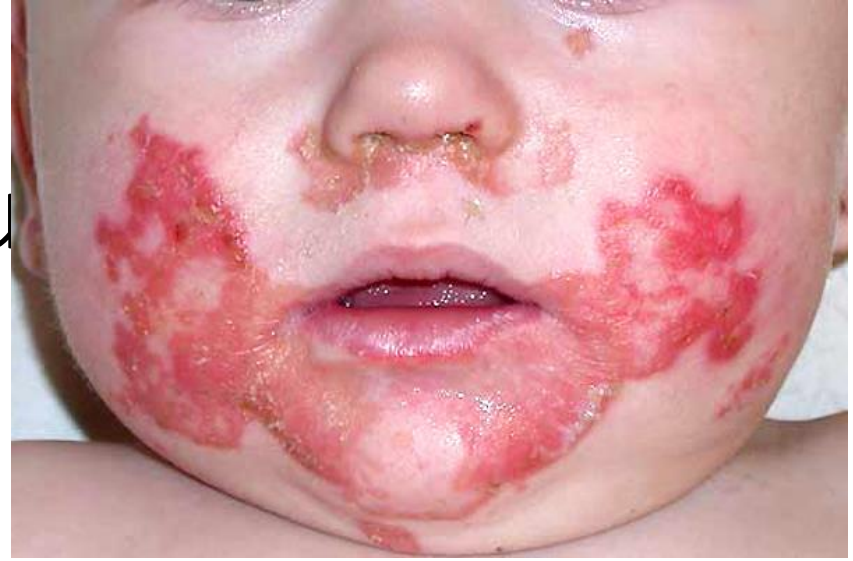
Alpha mannosidose



Smith Lemli Opitz Syndrome

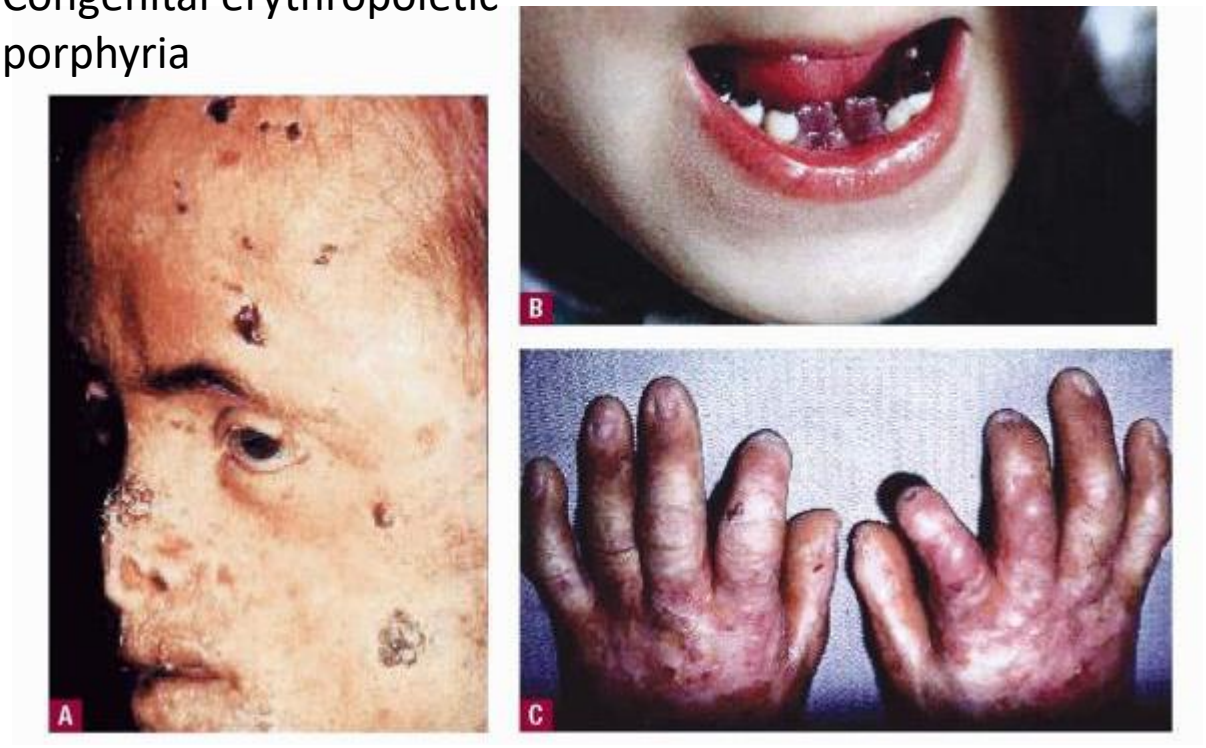


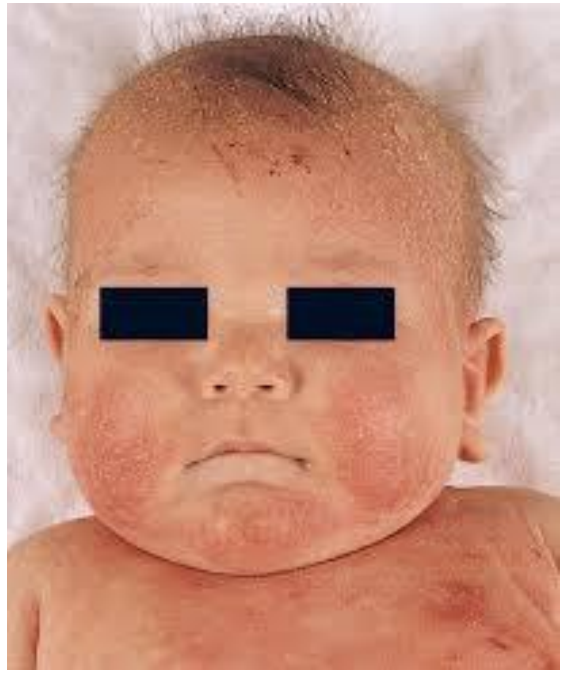
Oculocutaneous tyrosinemia (tyrosinemia type 2)



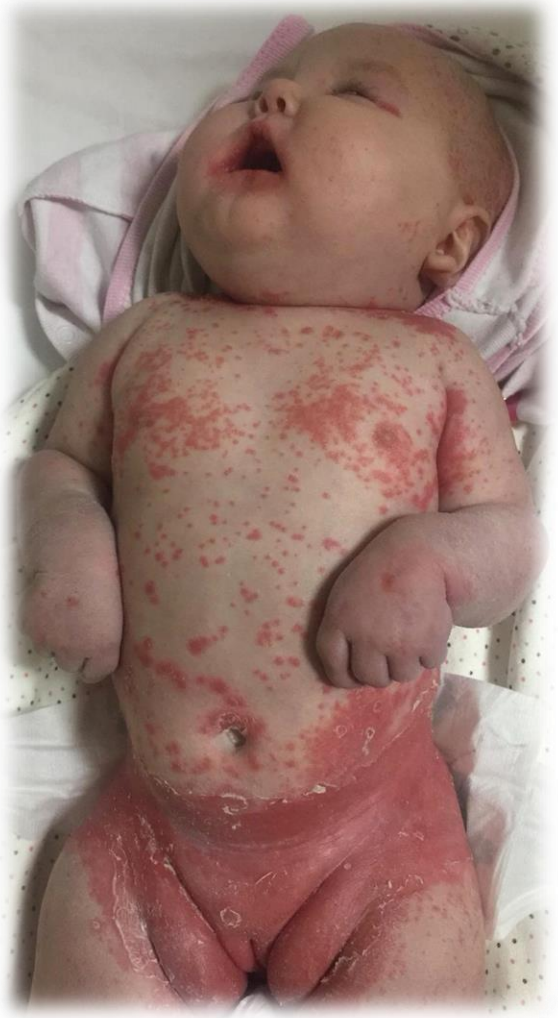
Acrodermatitis enteropathica

Congenital erythropoietic porphyria

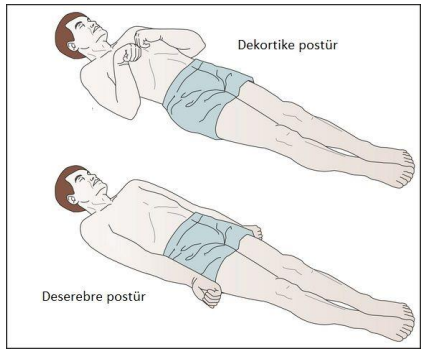


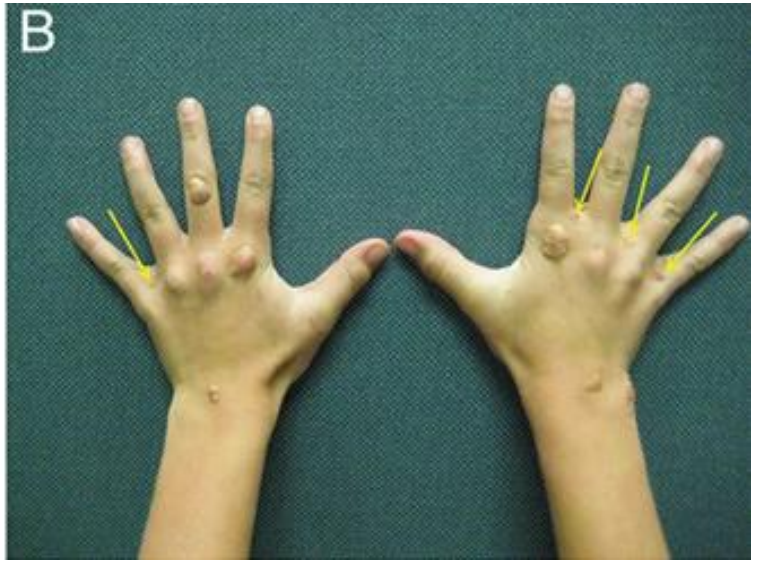


Multiple carboxylase deficiency (biotinidase or holocarboxylase synthetase deficiency)



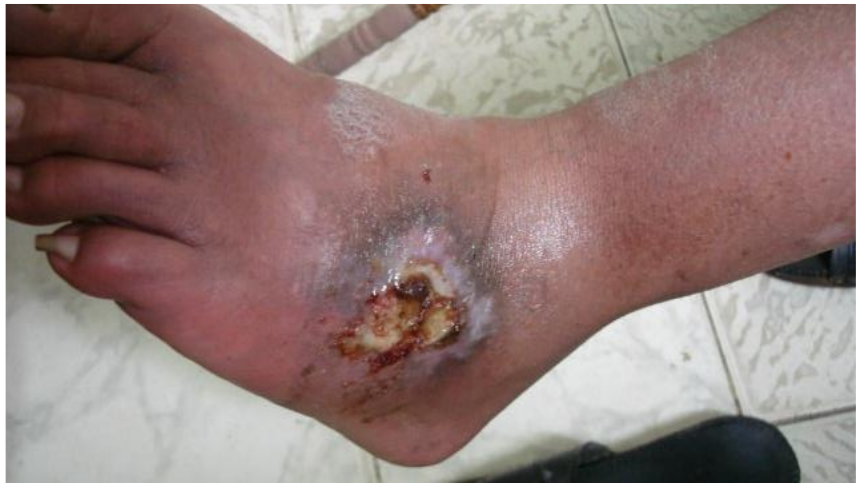
Biotinidase deficiency





Familial homozygous hypercholesterolemia

Prolidase deficiency

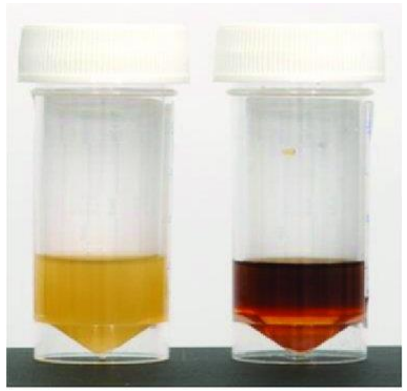


When Should We Think Metabolic Disease?

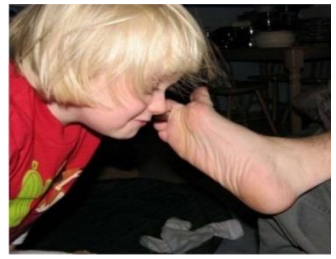
- **<u>Physical examination:</u>**
  - Hypotonia, hypertonia
  - Coma
  - Jaundice
  - Growth retardation
  - Cataracts, glaucoma, lens subluxation
  - Dysmorphism, atypical face, rough facial appearance
  - Seborrhea, photosensitive skin lesion
  - Skeletal anomaly
  - Myopathy, ataxia
  - Thromboembolic event, gangrene
  - Apnea, respiratory distress

When Should We Think Metabolic Disease?

- Abnormal urine color:
  - Alkaptonuria (black)
  - Porphyry (red)



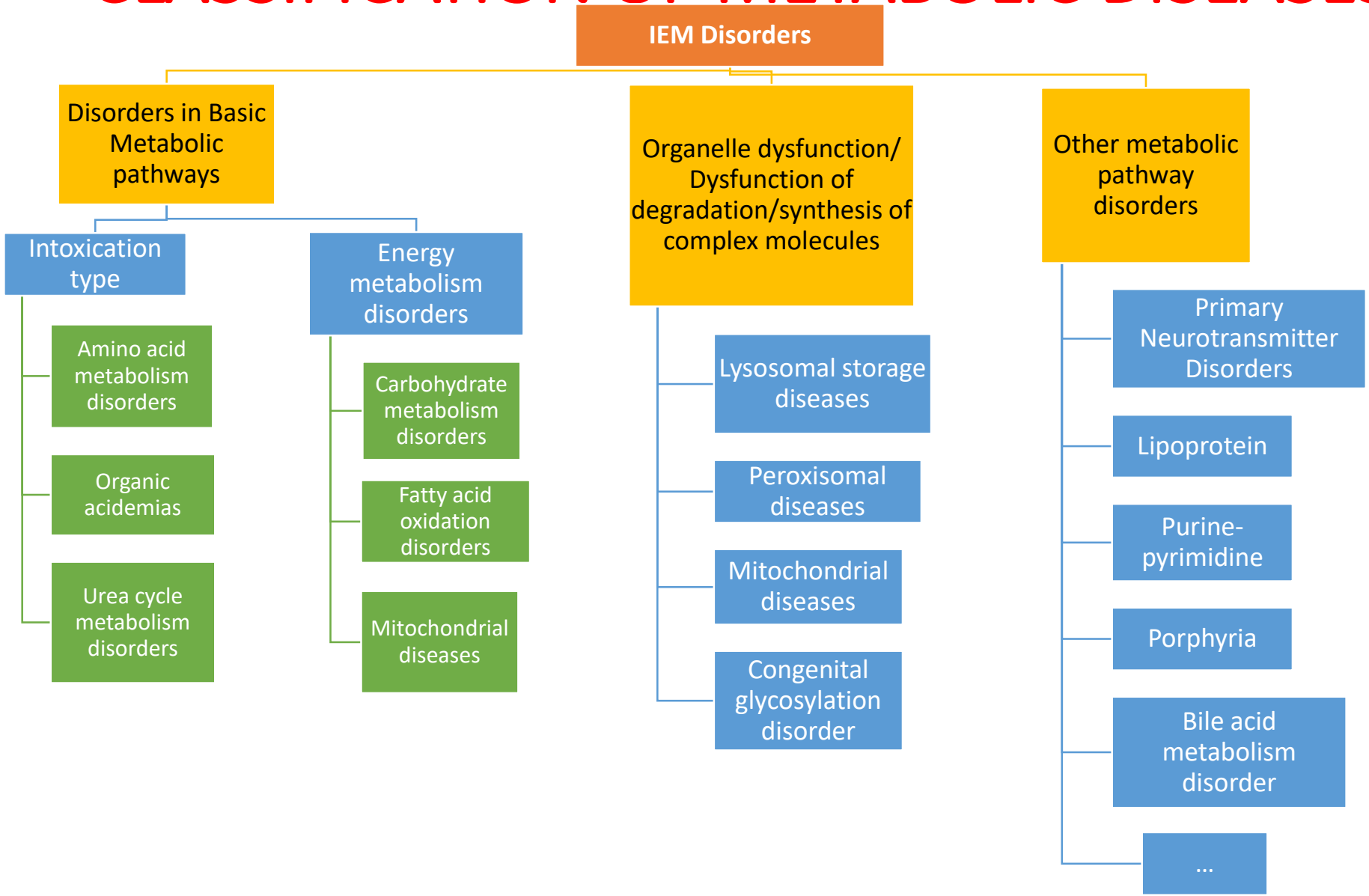
Odor	Disease
• Musty odor	Phenylketonuria
• Maple syrup odor	MSUD
• Sweaty feet	İsovaleric acidemia, GA II
• Tom cat urine	3-methylchrotonylglycinuria
	Multiple carboxylase defects
• Cabbage odor	Tyrosinemia Type 1
• Fish odor	Trimethylaminuria
	Dimethylglycinuria



Laboratory Findings

- Metabolic Acidosis
- Hyperammonaemia
- Respiratory alkalosis
- Hypoglycemia
- Ketosis
- Lactic acidosis
- Pyruvate increase
- Anemia
- Leukopenia
- Thrombocytopenia
- Low urea
- Low creatinine
- Low uric acid
- Elevated uric acid
- Low alkaline phosphatase
- Low cholesterol

CLASSIFICATION OF METABOLIC DISEASES



CLASSIFICATION OF METABOLIC DISEASES

- **Intoxication type**
- **Energy metabolism disorders**
- **Intracellular metabolism disorders**

Intoxication type

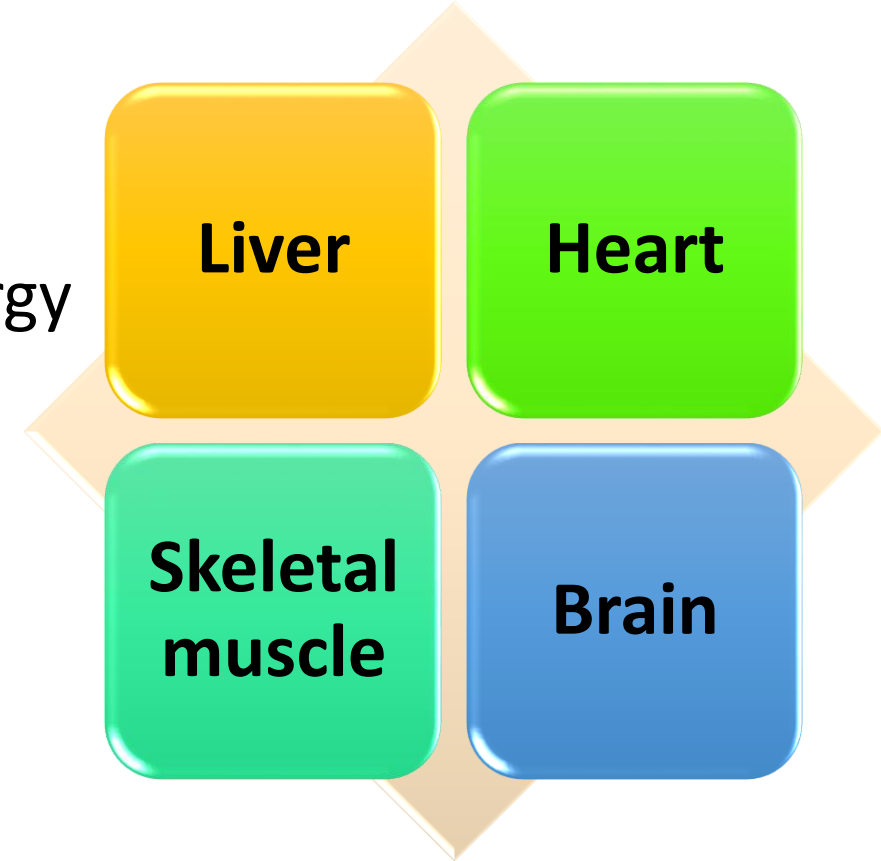
- Symptom-free period in which the patient appears healthy at the beginning
- Accumulation of toxic metabolites (hours / months)
- Acute / chronic intoxication picture, recurrent metabolic attacks
- Vomiting, lethargy, coma, liver failure
- Acidosis, ketosis, hyperammoniemia, hypoglycemia

Intoxication type

- Urea cycle metabolism disorder
- Organic acidemias (methylmalonic, propionic, isovaleric acidemia)
- Aminoacidopathies (PKU, MSUD, homocystinuria, tyrosinemia)
- Fatty acid oxidation defect
- Galactosemia
- Hereditary fructose intolerance

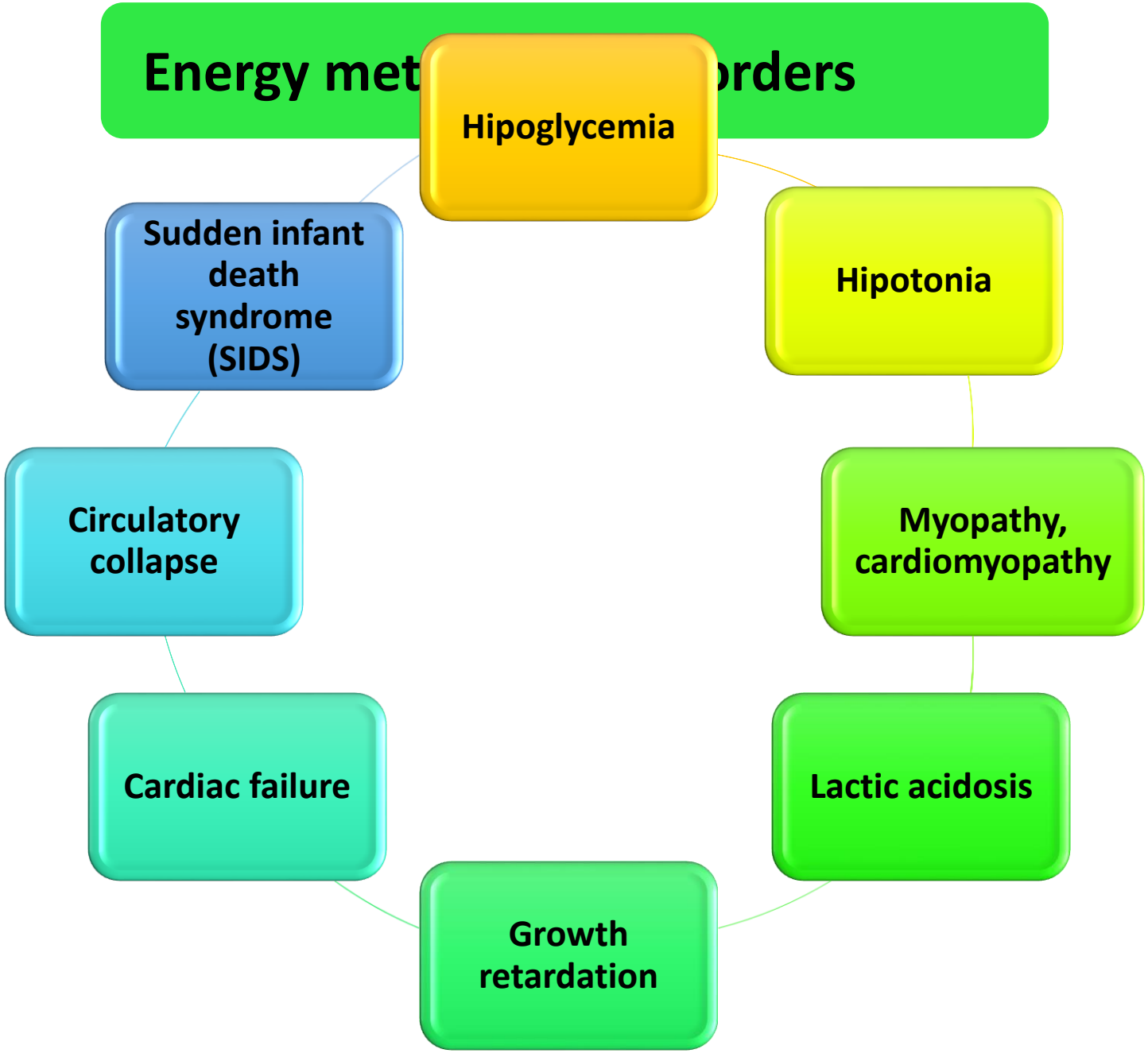
Energy metabolism disorders

- Impairment in biochemical reactions related to energy production and use
- The four main organs that consume energy



Energy metabolism disorders

- There is no symptom-free period in this type of disease, patients may be symptomatic immediately after birth.
- Diseases in which decreased fasting-tolerance
  - Glucose hemostasis disorder (GSH, gluconeogenesis defects)
  - Situations where alternative substrates cannot be synthesized when glycogen stores are used
    - Fatty acid oxidation defects, ketogenesis, ketolysis defects
- Disturbances in mitochondrial energy metabolism
  - Defects in the PDH complex
  - Respiratory chain defects
- Disturbances in Alternative Energy Sources
  - Creatine Deficiency Syndromes


Energy met orders
Hipoglycemia
Hipotonia
Myopathy, cardiomyopathy
Lactic acidosis
Growth retardation
Cardiac failure
Circulatory collapse
Sudden infant death syndrome (SIDS)

Intracellular metabolism disorders

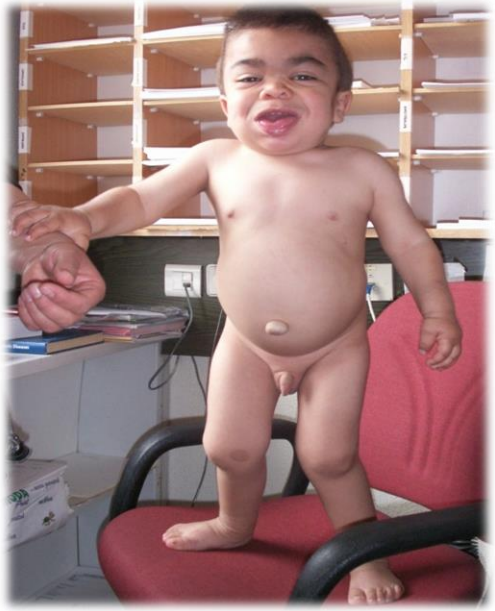
- In the synthesis or catabolism of complex molecules metabolic diseases that develop as a result of a disorder
  - Lysosomal diseases
  - Peroxisomal diseases
  - Congenital glycosylation disorders
  - Alpha-1 antitrypsin deficiencies

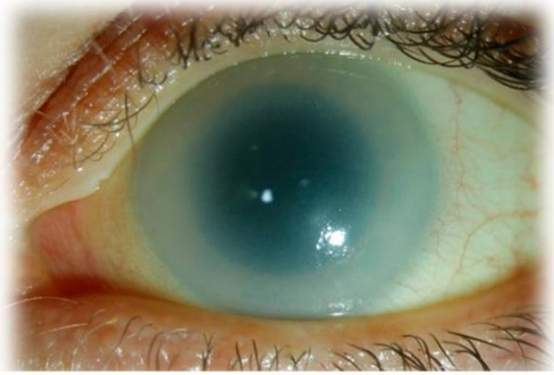
Intracellular metabolism disorders

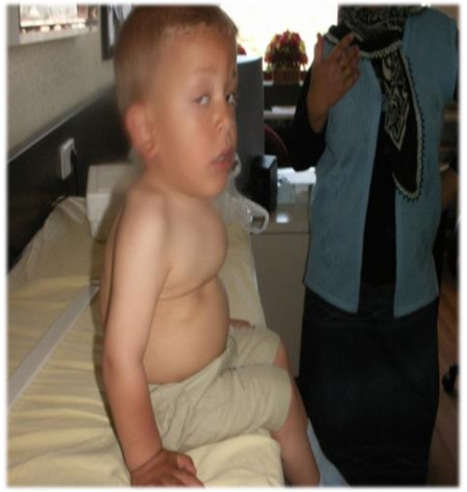
- Disturbances in intracellular synthesis and degradation of complex molecules
- Storage without metabolic imbalance
  - Lysosomal storage diseases
  - Gaucher disease
  - Niemann-Pick
  - Mucopolysaccharidoses
- Symptoms are persistent, progressive
- Protein loading, infections do not affect the clinical progress

Mucopolisaccaridosis

- Coarse facial
- Umbilical hernia
- Mental, motor retardation
- Corneal opacity
- Contractures
- Skeletal dysplasia
- Hepatosplenomegaly
- Deafness
- Diagnosis:
  - Dermatan, keratane, heparan sulfate in urine
  - Enzyme activity analysis
  - Genetic







Mucopolisaccaridosis

MPS type	Subtype and eponyms	Deficient enzyme	Gene (locus)	GAGS involved
MPS I	Hurler (H)	α-L-iduronidase	IDUA (4p16.3)	Dermatan, heparan sulfate
	Hurler/Scheie (H/S)			
	Scheie (S)			
MPS II	Hunter A	Iduronate sulfatase	IDS (Xq28)	Dermatan, heparan sulfate
	Hunter B			
MPS III	Sanfilippo A	Heparan-N-sulfatase	SGSH (17q25.3)	Heparan sulfate
	Sanfilippo B	α-N-acetylglucosaminidase	NAGLU (17q21)	
	Sanfilippo C	Heparan acetyl-CoA:α-glucosaminide N-acetyltransferase	HGSNAT (8p11.1)	
	Sanfilippo D	N-acetylglucosamine 6-sulfatase	GNS (12q14)	
MPS IV	Morquio A	Galactose 6-sulfatase	GALNS (16q24.3)	Keratan, chondroitin sulfate
	Morquio B	β-galactosidase	GLB1 (3p21.33)	Keratan sulfate
MPS VI	Maroteaux-Lamy	Arylsulfatase B	ARSB (5q11-q13)	Dermatan sulfate
MPS VII	Sly	β-glucuronidase	GUS (7q21.11)	Dermatan, keratin, chondroitin sulfate
MPS IX		Hyaluronidase 1	HYAL (3p21.3)	Hyaluronan

Enzyme Replacement Therapy in Lysosomal storage diseases

LSDs	Deficient enzyme	Inheritance	FDA approved ERT and Brand name
MPS I (Hurler syn.)	α-L-iduronidase	Autosomal	Laronidase (Aldurazyme™)/ 2003-FDA, EMA
MPS II (Hunter syn.)	Iduronate sulfatase	X-linked	Idursulfase (Elaprase™)/ 2006-FDA; 2007-EMA
MPS IV A (Morquio A syn.)	N-acetylgalactosamine 6-sulfatase	Autosomal	Elosulfase Alfa (Vimzim™)/ 2014-FDA
MPS VI (Marateaux-Lamy syn.)	N-acetylgalactosamine 4-sulfatase	Autosomal	Galsulfase (Naglazyme™)/ 2005-FDA; 2006-EMA
Fabry disease	α-galactosidase	X-linked	Agalsidase α (Fabrazyme™)/ 2001-EMA Agalsidase β (Replagal™)/ 2003-FDA, EMA
Pompe diseas	α-glucosidase	Autosomal	Aglucosidase (Myozyme™)/ 2006-FDA, EMA Aglucosidase (Lumizyme™)/ 2010-FDA
Gaucher disease	β -glucocerebrosidase	Autosomal	Aglucerase (Ceredase™)/ 1991-FDA Imiglucerase (Cerezyme™)/ 1994-FDA; 1997-EMA Velaglucerase (VPRIV™)/ 2010-FDA, EMA Taliglucerase (Elelyso™)/ 2012-FDA
Lysosomal acid lipase deficiency	Lysosomal acid lipase	Autosomal	Sebelipase α (Kanuma™)/ 2015-FDA,EMA

MPS: mucopolysaccharidosis; FDA: U.S. Food and Drug Administration; EMA: European Medical Agency.[1,5,7]


That's all Folks!