Neurometabolic Review

Pediatric Neurology Board Review 2024

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SAUDI BOARD RESIDENCY TRAINING PROGRAM

Pediatric Neurology Final Examination

Exam Format:

A Saudi board final specialty written examination shall consist of **two papers** each with **100-125** single best answer MCQs.

Up to 10% unscored MSQs can be added for calibration purposes.

Passing Score:

The passing score is **70%.** However, if the % of candidates passing the exam before final approval is <70%, the score must be lowered by 1 mark at a time aiming at achieving 70% passing rate or 65% passing score.

Under no circumstances can the passing score be reduced below 65%.

V24-27

The Neurological Disorders – Classification

1. Basic Neuroscience
2. Congenital Anomalies of the CNS
3. Cerebral palsy
4. Hypoxic-ischemic brain injury & cerebrovascular disease
5. Seizures & epilepsy
6. Neurological injuries (CNS vs PNS)
7. Developmental encephalopathy & neuropsychology
8. Neurogenetic / Neurocutaneous syndromes
9. Neurometabolic diseases
10. Movement disorders
11. Neurocritical care – Coma, brain death, acute encephalopathies
12. Headache
13. Neuro-immunology
14. Neuromuscular diseases
15. Neuro-infectious diseases
16. Neuro-oncology
17. Neuro-ophthalmology
18. Sleep disorders

Neurometabolic Review

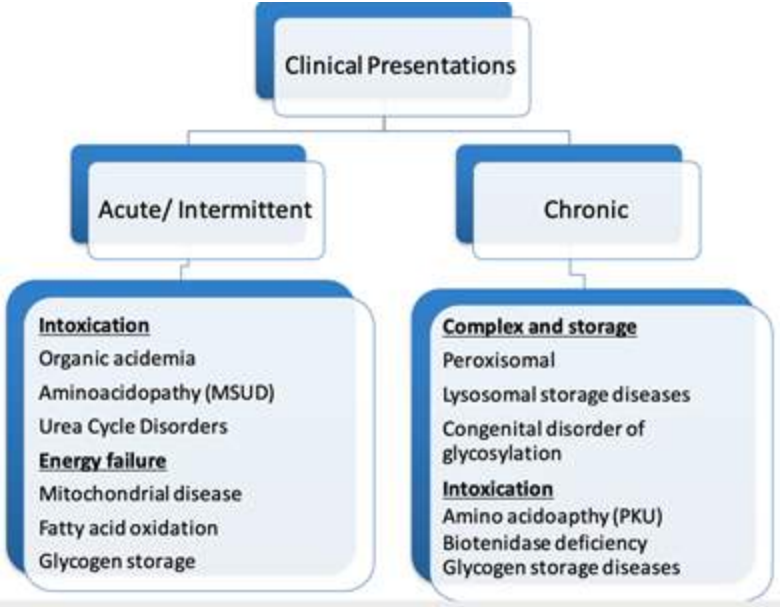
1. Introduction to IEM
2. Classification
   - Amino acid disorders (aminoacidopathies)
   - Organic acid disorders
   - Urea cycle defects
   - Disorders of Carbohydrate metabolism
   - Disorders of FA & ketone body metabolism
   - Disorders of energy substrate metabolism
   - Disorders of lipid metabolism
   - Disorders of lipoprotein metabolism
   - mtDNA-related disorders
   - Congenital disorders of glycosylation
   - Disorders of complex molecule degradation
   - Disorders of vitamin & cofactor metabolism
   - Disorders of trace elements & metals
   - Neurotransmitter disorders
3. Clinical Clues
4. Diseases included in the Saudi NBS
5. Treatment options

Part 1: Introduction

Inborn Errors of Metabolism

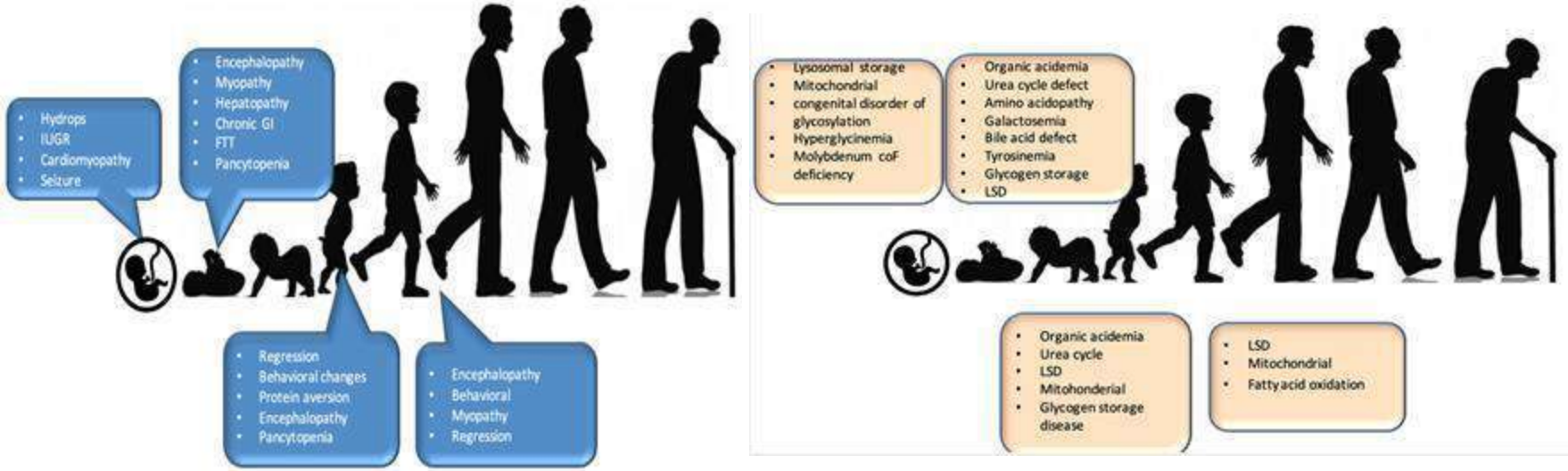
- Congenital metabolic disorders result from the absence or abnormality of an enzyme or its cofactor or, less frequently, a gene product that modulates the metabolic pathway through different mechanisms, such as substrate transport, leading to either accumulation or deficiency of a specific metabolite.
- There are > 600 condition
- Incidence 1:1000 Saudi (Saudi population 32,200 million 600,000 child born/year, 50-60% consanguinity).
- Single gene disorders (AR, AD, X-linked, Mitochondrial)
- It can present at any age but mainly during infancy.
- Onset can be Acute, Acute intermittent, and Chronic progressive.
- It has a multiorgan involvement but commonly affecting CNS, liver, Muscle, and kidneys

Clinical Presentation



Acute	Chronic
Seizure Encephalopathy Ataxia Behavioral or psychiatric symptoms Stroke	Intellectual disability Developmental delay Movement disorder (Dystonia) Abnormal body tone Irritability Regression
Examples	
Maple Syrup urine disease Organic acidemia Fatty acid oxidation deffect Urea Cycle defect Mitochondsrial disease	Phenylketonuria Homocystinuria Neurodegenerative brain disease Organic acidemia Urea cycle defect (Arginase deficiency) Pompe disease Zellweger syndrome

Age & Clinical Presentation



Classification

The traditional classification system for IEM groups the disorders according to the general type of metabolism involved. Some diseases fit into more than one category.
These major categories can be further grouped based upon similarities in pathogenesis and/or presenting features.

For an interactive version of the chart incorporating a zoom function, please refer to www.icimd.org.

Classification based on the biochemical features (type of molecule):

A) Small molecule disorders

- ➔ **Protein**: A.A. Disorders (amino-acidopathies), Organic Acid Disorders (Organic Acidemias, Organic Acidurias), Urea Cycle Defects.
- ➔ **Fat**: Fatty acid oxidation disorders (FAOD).
- ➔ **Sugar**: Glucose, galactose, fructose.

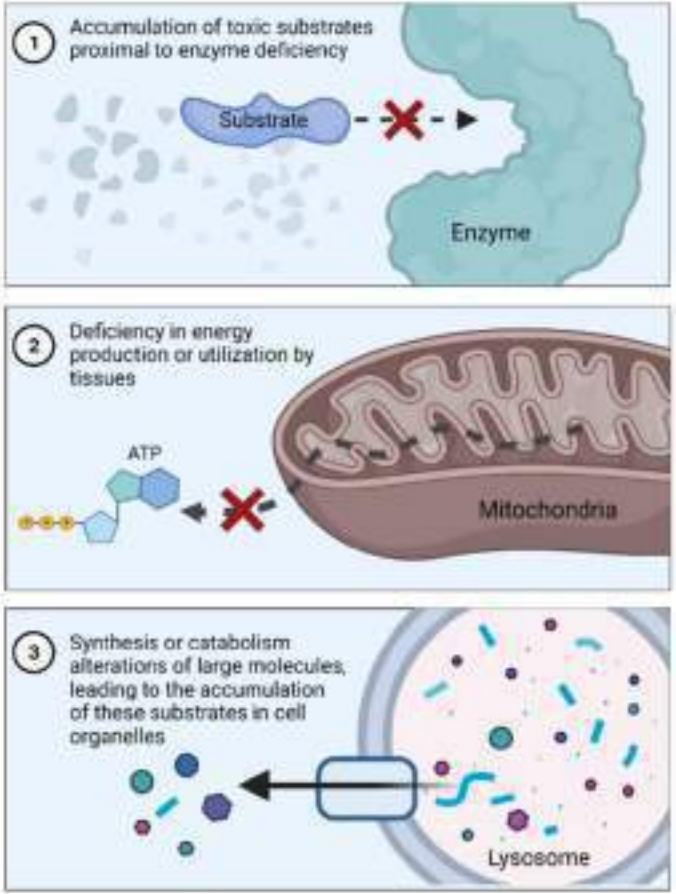
B) Large molecule disorders

- ➔ **Peroxisomal**
- ➔ **Lysosomal**

Classification based on pathophysiology:

Inborn Errors of Metabolism (IEM) Nosological Classification

1. Intoxication Disorders
2. Energy Metabolism Disorders
3. Storage Diseases



Solares I, Heredia-Mena C, Castelbón FJ, Jericó D, Córdoba KM, Fontanellas A, Enríquez de Salamanca R, Morales-Conejo M. Diagnosis and Management of Inborn Errors of Metabolism in Adult Patients in the Emergency Department. Diagnostics. 2021

Classification based on pathophysiology:

The IEM can be divided into three broad categories:

A) **Disorders of acute or progressive intoxication or encephalopathy:**

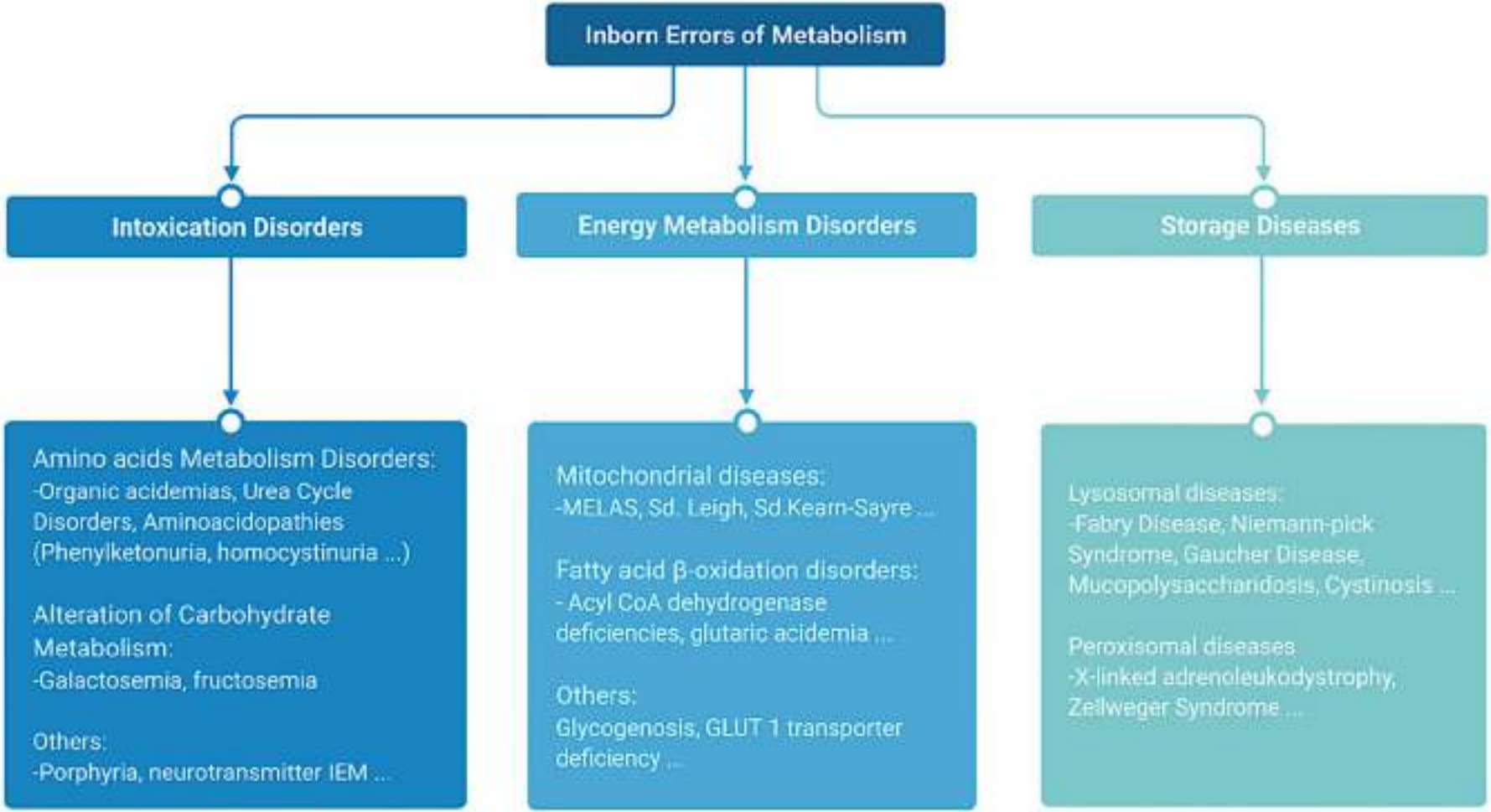
- Symptoms are caused by accumulation of toxic compounds proximal to the metabolic block.
- Symptom-free interval followed by clinical signs of intoxication with metabolic disturbances.
- This category includes: A.A. disorders, most organic acidemias, UCDs, and carbohydrate intolerance (eg, galactosemia, hereditary fructose intolerance).

Classification based on pathophysiology:

B) Disorders associated with energy deficiency:

- Symptoms are caused by deficiency in energy production or utilization in the liver, myocardium, skeletal muscle, or brain.
- Signs or symptoms related to accumulation of toxic compounds.
- This category includes disorders of glycogenolysis and gluconeogenesis, fatty acid oxidation defects, disorders of ketogenesis, and mitochondrial disorders.

C) Disruption of complex molecule metabolism: Defects in the catabolism of complex molecules in cell organelles, e.g. lysosomal storage disorders or peroxisomal disorders.

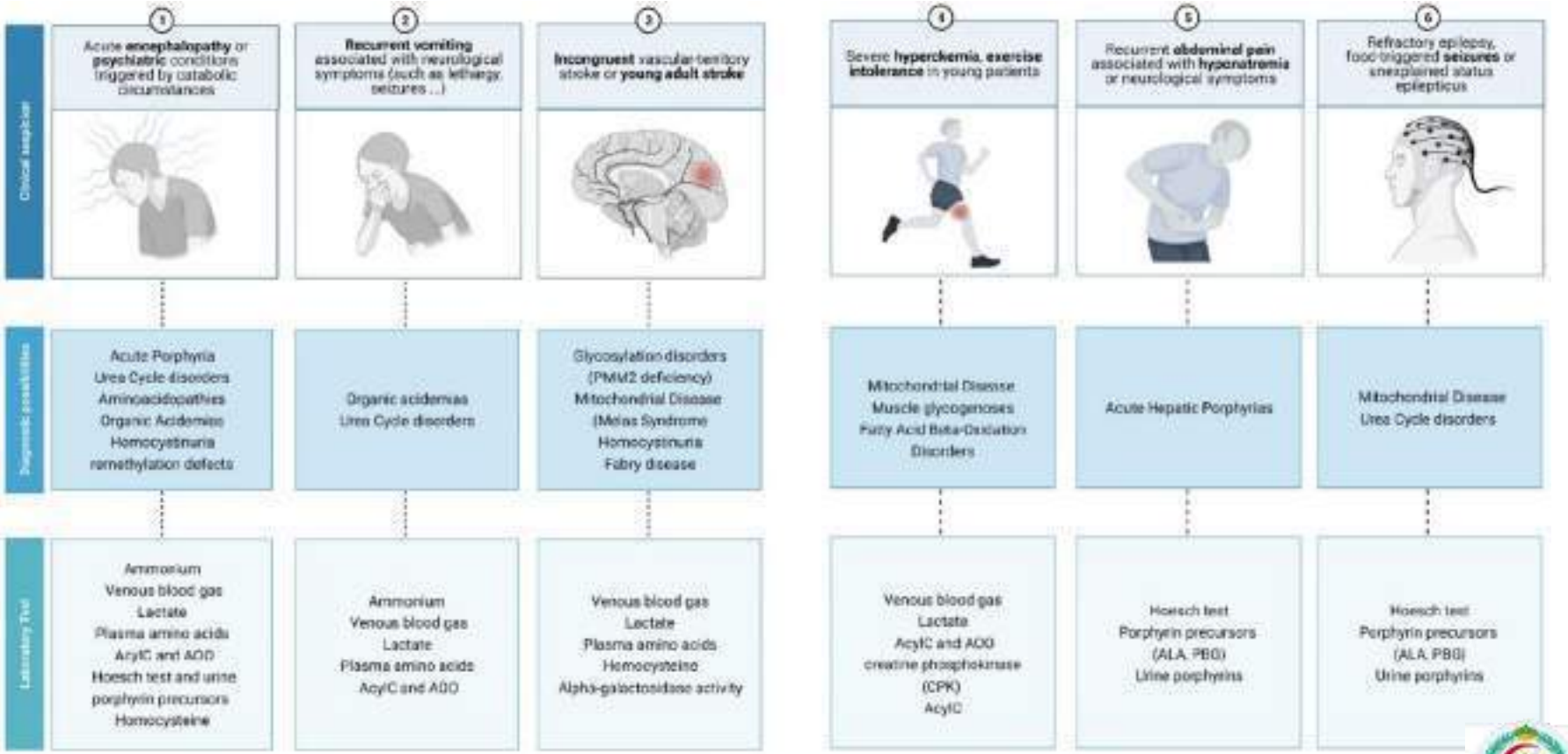

Inborn Errors of Metabolism
Intoxication Disorders
Energy Metabolism Disorders
Storage Diseases
Amino acids Metabolism Disorders:
-Organic acidemias, Urea Cycle Disorders, Aminoacidopathies (Phenylketonuria, homocystinuria ...)
Alteration of Carbohydrate Metabolism:
-Galactosemia, fructosemia
Others:
-Porphyria, neurotransmitter IEM ...
Mitochondrial diseases:
-MELAS, Sd. Leigh, Sd.Kearn-Sayre ...
Fatty acid β-oxidation disorders:
- Acyl CoA dehydrogenase deficiencies, glutaric acidemia ...
Others:
Glycogenosis, GLUT 1 transporter deficiency ...
Lysosomal diseases:
-Fabry Disease, Niemann-pick Syndrome, Gaucher Disease, Mucopolysaccharidosis, Cystinosis ...
Peroxisomal diseases
-X-linked adrenoleukodystrophy, Zellweger Syndrome ...

Classification based on pathophysiology:

Pathophysiologic Effects	Examples	Appearance at Birth	Triggers (Illness, Protein Load)	Diagnosis Made by Available Metabolic Screening Tests	Treatable
Metabolite accumulation and intoxication	Organic acid disorders, urea cycle defects, aminoacidopathies	Usually normal	Often	Often	Often
Impairment of energy metabolism	Mitochondrial disorders, fatty acid oxidation disorders	Sometimes normal but may affect metabolically active tissues (eg, brain malformation)	Often	Sometimes; may need enzyme or DNA testing	Sometimes
Disruption of complex molecule metabolism	Peroxisomal disorders, lysosomal disorders	Sometimes normal, but some present with dysmorphology or organomegaly	Rare	Rarely; diagnosis usually requires specialized enzyme or DNA testing	Rare

DNA = deoxyribonucleic acid.

When should we consider an IEM?



When should we consider an IEM?

(1) Recurrent attacks of **encephalopathy**, vomiting, ataxia, and **metabolic acidosis**, especially when the attacks appear to be **triggered by illness or changes in diet** (since both catabolism and increased protein intake can provoke metabolic deterioration).
(2) Progressive or **chronic symptoms** of failure to thrive, weakness, or developmental delay.
(3) **Unusual organ dysfunction** such as cardiomyopathy, hepatomegaly, skeletal findings, or lens dislocation.

The Categories of IEM:

1. **Amino acid disorders (aminoacidopathies):** PKU, homocystinuria, MSUD, hartnup, NKH
2. **Organic acid disorders:** PA, MMA, IVA, MCD (biotinidase), glutaric aciduria 1
3. **Urea cycle defects:** OTC, CPS, NAGS, citrullinemia (ASSD), ASLD, ARG
4. **Disorders of carbohydrate metabolism:** Glucose (GSD), galactose (galactosemia), fructosemia
5. **Disorders of fatty acid & ketone body metabolism:** FAOD, carnitine d, glutaric acidemia II
6. **Disorders of energy substrate metabolism:** PCD
7. **Disorders of lipid metabolism:** X-linked adrenoleukodystrophy
8. **Disorders of lipoprotein metabolism:** HDL, LDL and/or triglycerides
9. **mtDNA-related disorders:** Single large-scale mtDNA deletions (Kearns–Sayre syndrome)
10. **Congenital disorders of glycosylation**: Type ! and II
11. **Disorders of complex molecule degradation:** Sphingolipid, GAG, glycoprotein, NCL, others
12. **Disorders of vitamin & cofactor metabolism:** Tetrahydrobiopterin, thiamine, pantothenate and CoA, pyridoxine, biotin, cobalamin, molybdenum cofactor.
13. **Disorders of trace elements & metals:** Copper, iron, zinc metabolism

The Categories of IEM:

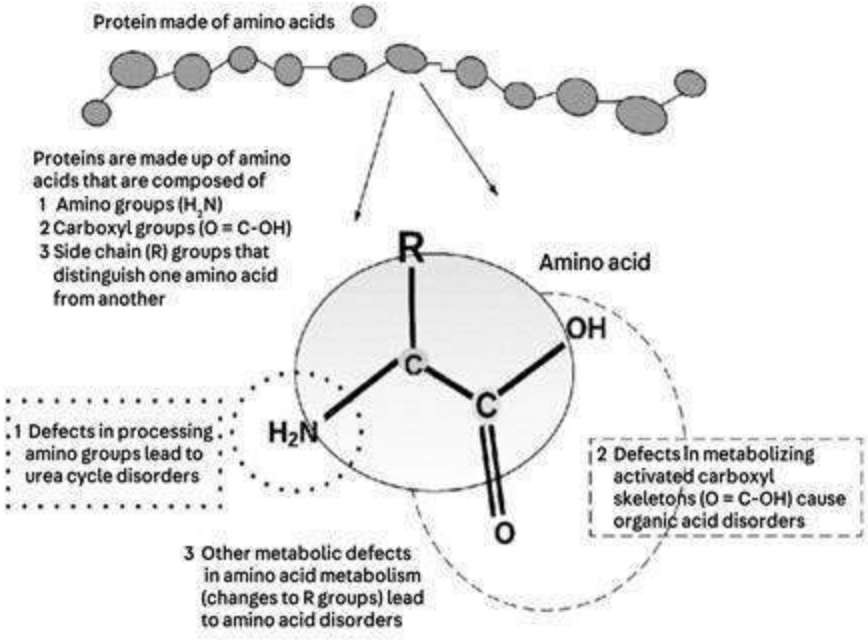


FIGURE 2-1

Metabolism of amino acids occurs by deamination or removal of the amino group (urea cycle disorders), metabolism of the carboxyl skeleton of the amino acid (organic acid disorders), or transformation into other amino acids or compounds (amino acid disorders).

Part 2: Disorders & MCQs

The Categories of IEM:

1. **Amino acid disorders (Aminoacidopathies):** PKU, homocystinuria, MSUD, hartnup, NKH
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13. **Disorders of trace elements & metals:** Copper, iron, zinc metabolism
14. **Disorders of nucleobase, nucleotide and nucleic acid metabolism:** Disorders of purine metaboli

I. AMINO ACID DISORDERS (AMINOACIDOPATHIES)

A.A. disorders are caused by a defect in the metabolic pathways of A.A.

They are called amino acidemias when there is abnormal accumulation of A.A. in the plasma and amino acidurias when there is abnormal excretion of A.A. in the urine.

Symptoms result from accumulation of the substance that cannot be metabolized.

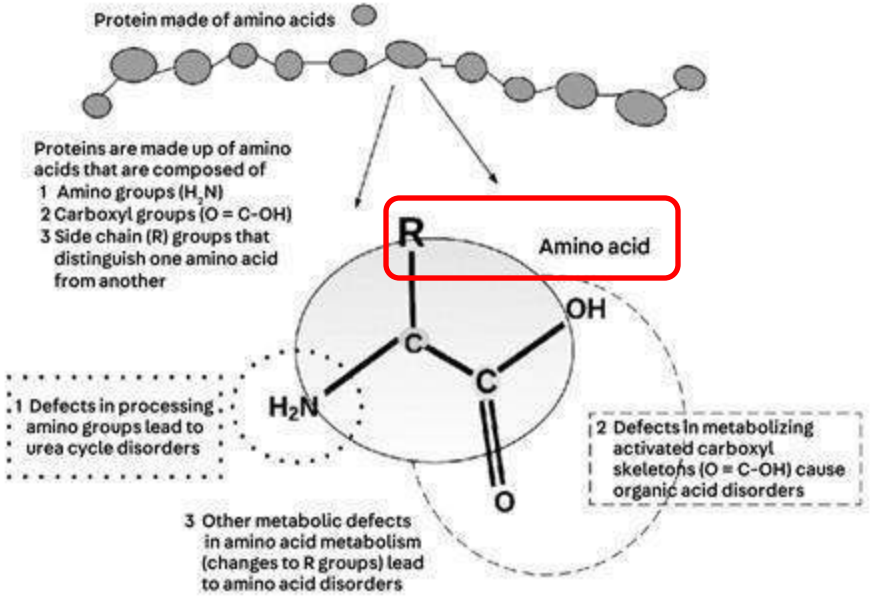


FIGURE 2-1
Metabolism of amino acids occurs by deamination or removal of the amino group (urea cycle disorders), metabolism of the carboxyl skeleton of the amino acid (organic acid disorders), or transformation into other amino acids or compounds (amino acid disorders).

I. AMINO ACID DISORDERS (AMINOACIDOPATHIES)

- All are inherited as **AR** traits.
- They usually have normal gas except **MSUD** (behaves as an organic acidemia)
- A.A. disorders are characterized by early encephalopathy, usually without metabolic acidosis, but the nature of the encephalopathy and clinical presentation vary.
- A.A. disorders often present in newborns who are initially well and become acutely symptomatic (metabolic decompensation; poor feeding and lethargy) after a period of protein feeding.
- In older children, developmental delay or regression is usually present.

I. AMINO ACID DISORDERS (AMINOACIDOPATHIES)

Disorders of phenylalanine and tyrosine metabolism	**Phenylketonuria**
Disorders of the metabolism of sulfur-containing AA and hydrogen sulfide	**Homocystinuria or Cystathionine beta-synthase deficiency**
Disorders of BCAA metabolism (considered OA)	**Maple Syrup Urine Disease (MSUD)**
Disorders of amino acid transport	**Hartnup disorder**
Disorders of glycine and serine metabolism	**Nonketotic hyperglycinemia due to glycine decarboxylase deficiency**

I. AMINO ACID DISORDERS (AMINOACIDOPATHIES)

- Biochemical findings that may be present in amino acid disorders include metabolic acidosis, hyperammonemia, hypoglycemia with appropriate or increased ketosis, liver dysfunction.
- +/- Reducing substances in the urine.
- A.A. disorders can be detected by newborn screening using tandem mass spectrometry.
- Confirmation of diagnosis involves measurement of quantitative plasma A.A. and qualitative urine organic acids and enzyme analysis.

Test Name	Conditions Screened
Ammonia	Urea cycle defects, organic acidurias
Plasma amino acids	Aminoacidopathies, urea cycle disorders, some organic acidurias
Urine organic acids	Organic acidurias
Plasma acylcarnitine profile	Organic acidurias, fatty acid oxidation defects

1. Phenylketonuria (PKU)

Diagnosis:

- Newborn screening detects hyperphenylalaninemia
- Genetics molecular analysis of the phenylalanine hydroxylase gene
- **Tetrahydrobiopterin** is a cofactor for phenylalanine hydroxylase, and its deficiency may produce hyperphenylalaninemia (PKU-like).

Treatment:

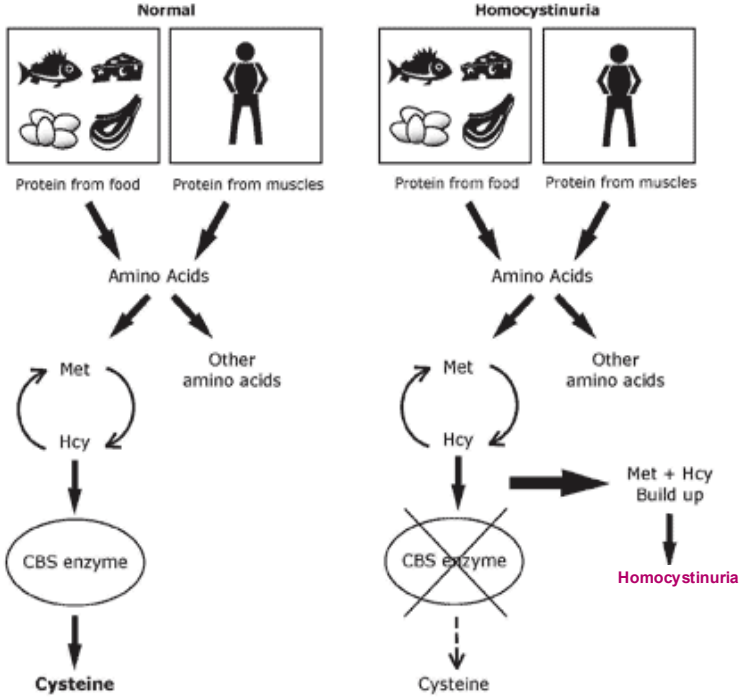
- Dietary restriction of phenylalanine
- **Low-protein diet**
- Phenylalanine-free feeding formula after birth, which will prevent neurologic deterioration.
- Tetrahydrobiopterin is used as a treatment adjunct in select patients.

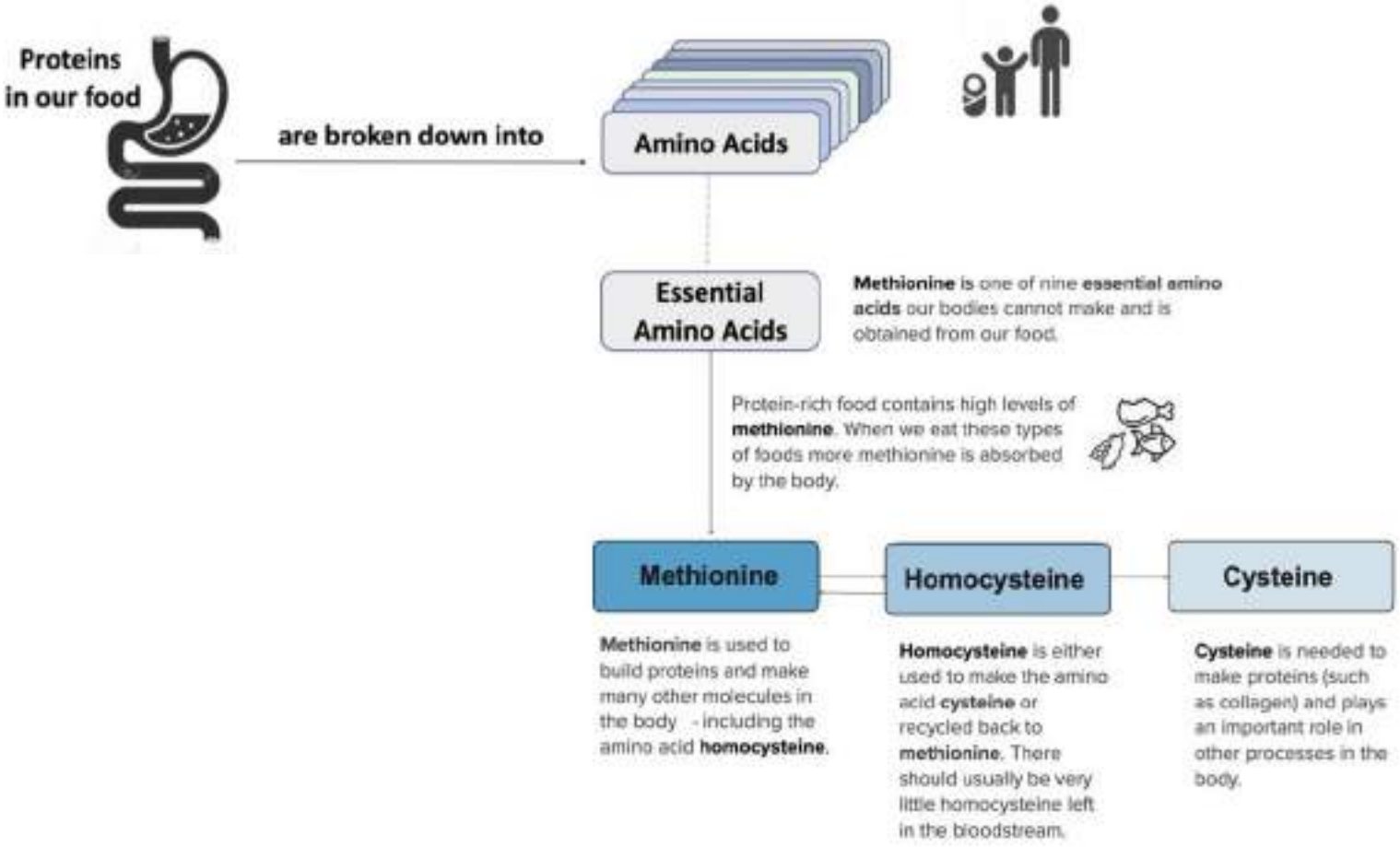
Prognosis: With treatment, there will be a ↓ in: eczematous flare-ups, osteopenia, and visual abnormalities. Despite treatment, some patients still have varying degrees of cognitive delays.

2. Homocystinuria

Homocystinuria is an **AR** condition caused by mutations in the **gene CBS at 21q22.3** that encodes the enzyme **cystathionine-β-synthase.**

Deficiency of this enzyme produces an **elevation** of **blood and urine levels** of **homocystine**, **homocysteine**, and **methionine**.




Proteins in our food
are broken down into
Amino Acids
Essential Amino Acids
Methionine is one of nine essential amino acids our bodies cannot make and is obtained from our food.
Protein-rich food contains high levels of methionine. When we eat these types of foods more methionine is absorbed by the body.
Methionine
Homocysteine
Cysteine
Methionine is used to build proteins and make many other molecules in the body - including the amino acid homocysteine.
Homocysteine is either used to make the amino acid cysteine or recycled back to methionine. There should usually be very little homocysteine left in the bloodstream.
Cysteine is needed to make proteins (such as collagen) and plays an important role in other processes in the body.

2. Homocystinuria

- **Homocysteine**, when condensed with **serine**, can be converted to **cystathionine**, a step catalyzed by the enzyme **cystathionine-β- synthase.**
- **Cystathionine** is subsequently converted to **cysteine** and then **cystine**.
- Homocysteine can also be methylated to **methionine**, a step that requires **folate** and **vitamin B12.**

2. Homocystinuria

Two variants

(1) **Pyridoxine responsive** (some residual activity of the cystathionine-β-synthase)
(2) **Non pyridoxine responsive**

Two genotypes

(1) **Heterozygous** mutations lead to **accelerated atherosclerosis.**
(2) **Homozygous** mutations lead to **increased platelet aggregation.**

Three subtypes

(1) **Cystathionine 13-synthase deficiency:** Homozygous mutations may result in strokes, MI, intellectual disability, glaucoma, lens dislocations, a marfanoid body type, and osteoporosis. Symptom onset occurs prior to age five.
(2) **Methylene-tetrahydrofolate reductase (MTHFR) deficiency:** More severe phenotype.
(3) **Deficiency of B12 coenzyme** synthesis and transport.

2. Homocystinuria

CYSTATHIONINE BETA-SYNTHASE (CBS) DEFICIENCY

Other names for this form of homocystinuria include:

- Homocystinuria due to cystathionine beta-synthase deficiency
- Cystathionine β-synthase deficiency
- CBS deficiency
- Classic homocystinuria
- Classical homocystinuria
- Homocystinuria (HCU)

SEVERE METHYLENETETRAHYDRO-FOLATE REDUCTASE (MTHFR) DEFICIENCY

Other names for this form of homocystinuria include:

- Homocystinuria due to methylenetetrahydro-folate reductase deficiency
- 5,10 alpha methylenetetrahydro-folate reductase deficiency
- MTHFR deficiency

COBALAMIN C DISEASE (CBLC)

Other names for this form of homocystinuria include:

- Methylmalonic acidemia with homocystinuria (MMA+HCU) cblC
- Methylmalonic aciduria and/with homocystinuria cblC
- Cobalamin C disease
- cblC

2. Homocystinuria

(Cystathionine beta-synthase deficiency)

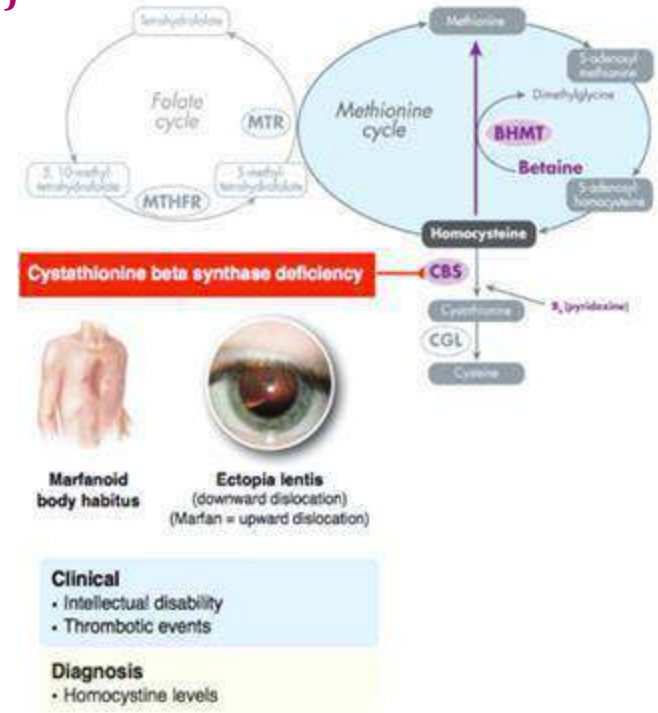
Clinical Presentation:

Status at birth	Normal at birth
CNS	Seizures
Developemntal, cognition, & behavior	Developmental delay, intellectual disability, and psychiatric manifestations
MSK	Marfanoid habitus with tall and thin stature Pectus carinatum, pes cavus, and genu valgum Scoliosis and crush vertebral fractures are common Abnormal gait (Charlie Chaplin gait)
Eyes	Ectopia lentis and lens dislocation
Collagen metabolism abnormality	Eye, bones, and the vascular system: Intimal thickening of the blood vessel walls and high incidence of thromboembolism, including strokes.
Endocrine	Osteoporosis

2. Homocystinuria

(Cystathionine beta-synthase deficiency)

Marfan Syndrome	Classical Homocystinuria
Autosomal **DOMINANT**, FBN1 mutation on chromosome 15	Autosomal **RECESSIVE**, CBS mutation on chromosome 21
HYPEREXTENSIBLE joints, **UPWARD** dislocation of ocular lense	**RIGID** joints, **DOWNWARD** dislocation of ocular lense
Aortic root **DILATION/DISSECTION**, valvular insufficiency	**VASO-OCCLUSIVE** disease
Diagnosis is made with the revised **GHENT** criteria	Diagnosis is made with high plasma/urine levels of **HOMOCYSTEINE** and **METHIONINE**
Aortic aneurysm is treated with **β-BLOCKERS ± SURGERY**	Primarily treated with high dose vitamin B_6



2. Homocystinuria

(Methylenetetrahydro-folate reductase deficiency)

Definition:

- the most common metabolic disorder of folate metabolism.
- It is characterized by hyperhomocysteine- mia, with elevated plasma S-adenosylhomocysteine, homocystin- uria, increased plasma cystathionine, as well as low/normal plasma methionine and S-adenosylmethionine (AdoMet).

Phenotype:

- Due to the large number of private mutations, genotype– phenotype correlations or correlations between type or location of mutation and clinical course have so far not been established in MTHFR deficiency.
- Based on the residual activity and age of onset (early: <1 year; late >1 year).

Diagnosis:

- Elevated plasma total homocysteine
- Plasma methionine is high in classical homocystinuria VS low or low–normal in MTHFR deficiency.
- Plasma cystathionine is decreased in CBS deficiency, VS elevated in MTHFR deficiency.

2. Homocystinuria

(Methylenetetrahydro-folate reductase deficiency)

Treatment:

- Causal treatment for MTHFR deficiency is not available.
- **Betaine** is the mainstay of symptomatic treatment (Early treatment has been shown to prevent neurocognitive decline in patients with MTHFR deficiency). *Note: Brain edema has been reported as a side effect of betaine treatment in 2 with classical homocystinuria.*
- Supplemental **methionine** may add clinical benefit (No clinical trials).
- In theory, **riboflavin** could be an additional therapeutic option (No clinical trials).
- Folinic acid or methylTHF have **NOT** been convincingly shown to improve the clinical course in MTHFR deficiency.
- Folic acid should be avoided in MTHFR deficiency since it may aggravate the deficit of methylTHF in the CNS.
- Nitrous oxide, which inhibits methionine synthase, may cause acute clinical deterioration and is contraindicated in patients with MTHFR deficiency.

3. Maple Syrup Urine Disease (MSUD)

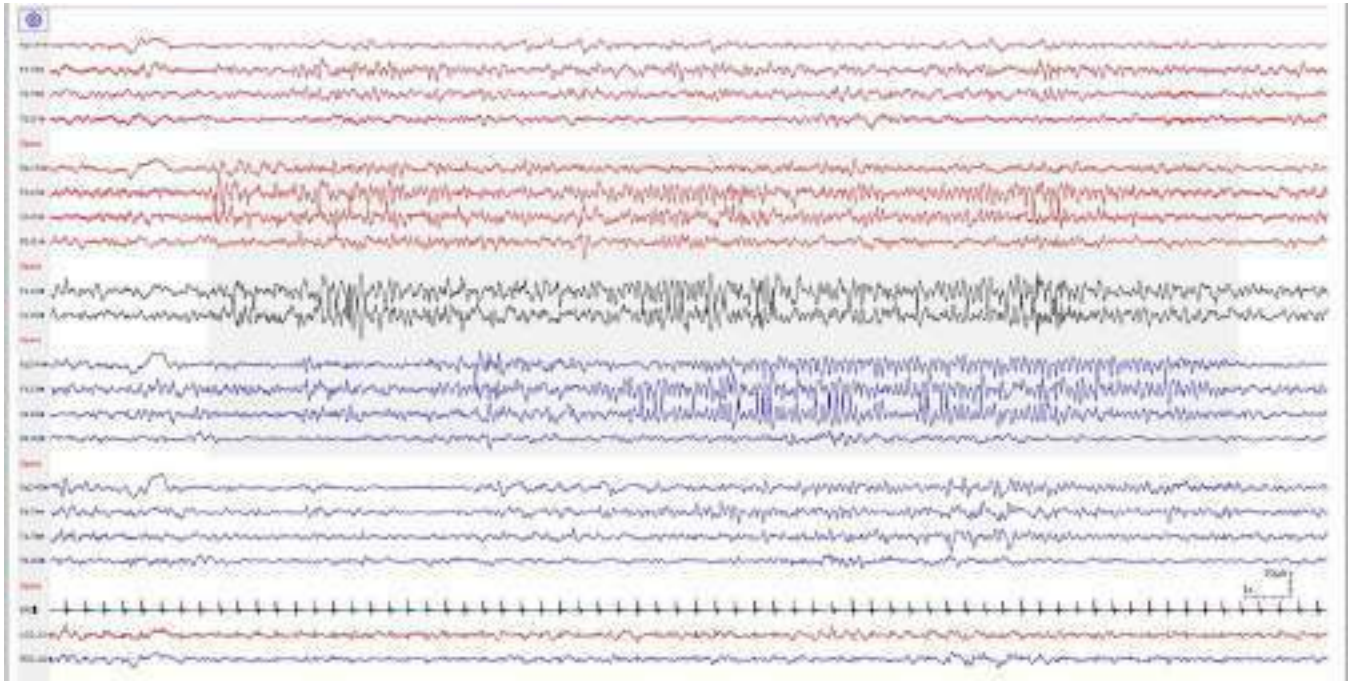
Definition:
The branched-chain amino acids (BCAA) (**leucine**, **isoleucine**, and **valine)**, are normally transformed to α-ketoacids -> catabolized by oxidative decarboxylation by **branched-chain α-ketoacid dehydrogenase complex**.

Etiology:
MSUD is caused by **branched-chain α-ketoacid dehydrogenase complex** deficiency, leading to the accumulation of **branched amino acids (isoleucine, leucine, and valine)** and their ketoacids.

MOI: AR

Characteristic:
During an episode, the urine has a maple syrup smell and is made dark by blood and urine containing high levels of branched-chained amino acids and ketoacids.

3. Maple Syrup Urine Disease



An illustration of the "comb-like" pattern as frontocentral 7 Hz non-evolving rhythmic activity, symmetrical between the hemispheres but asynchronously starting over the left central area then becoming more prominent over the right central area after 8 s. This tracing is usually observed during the clinical deterioration and worsening metabolic encephalopathy.

3. Maple Syrup Urine Disease

Diagnosis:

- **Prenatal**: branched-chain alpha-ketoacid dehydrogenase complex enzyme activity **OR** DNA testing for gene mutation
- **At birth**: Newborn screening
- **After 6 days of age**: Detection of elevated levels of BCAA and their ketoacids in blood and urine. **OR** Enzyme activity can be measured in fibroblasts and hepatocytes.

MRI: Dysmyelination, heterotopias, diffuse spongy degeneration, and a failure of cortical lamination

Treatment:

- Hemodialysis and **diets low in branched-chain amino acids** are the treatment of choice.
- A thiamine responsive variant exists; hence a trial of thiamine is warranted.
- Liver transplantation.

3. Maple Syrup Urine Disease

Maple Syrup Urine Disease

[Branched-chain ketoaciduria]

Branched-chain amino acids

- Leucine
- Isoleucine
- Valine

Enzyme defect: **Branched-chain ketoacid dehydrogenase**

Newborns develop ketonuria within 48 hrs of birth

Clinical

- Irritability
- Poor feeding
- Vomiting
- Lethargy
- Dystonia
- Seizures
- Cerebral edema

Diagnosis

- Prenatal: Measure branched-chain alpha-ketoacid dehydrogenase complex activity
- Newborn screening: Tandem mass spectrometry

Management

- Dietary therapy to promote normal growth and development
- Aggressive treatment of episodes of acute metabolic decompensation

4. Hartnup disorder

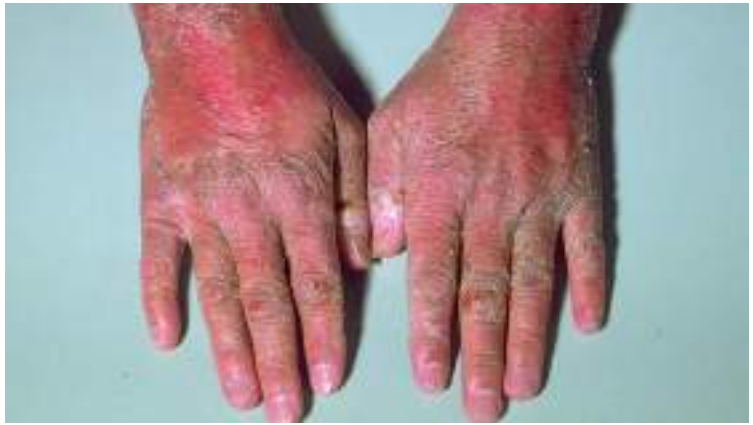
Definition: Hartnup disease results from an abnormality of the **neutral amino acid transport protein**, such that it impairs intestinal and renal absorption of neutral amino acids (i.e. **tryptophan**).

MOI: AR inheritance, with a mutation on chromosome **5.** Gene is SLC6A19
- Low tryptophan levels lead to secondary niacin deficiency

Presentation:

- Symptoms are unrelated to diet, and include **photosensitive pellagra-like dermatitis** (due to **nicotinamide deficiency**), developmental delays, headaches, psychiatric changes, hypotonia, and ataxia.
- Clinical presentations may be due in part to intestinal absorption of toxins resulting from amino acid breakdown.
- Stress or infection can trigger symptomatic episodes, and take up to 1 month for resolution.

4. Hartnup disorder

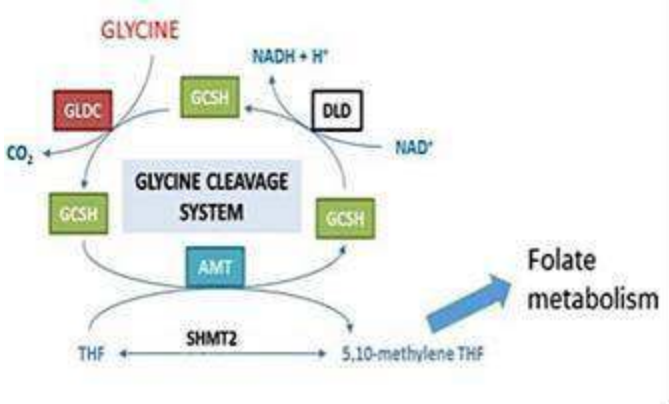


TTT:

- - Daily oral administration of nicotinamide (**NAD**), 50–300 mg, may reverse the skin and neurological complications.
- - A high-protein diet helps make up for the amino acid loss

5. Nonketotic hyperglycinemia (NKH) or Glycine encephalopathy

Definition:
NKH is caused by a **defect in one of three proteins** that together make up the mitochondrial glycine cleavage system, resulting in complete absence of function and the accumulation of glycine in all body tissues.



MOI: AR

Etiology: PTH
The most common mutation occurs in the **P-protein** (glycine decarboxylase gene, **GLDC**, **9p24.1**) = (**70% to 75%**)
Mutations in the **T-protein** (**aminomethyltransferase**, **AMT** gene, **3p21.31**) = 20%
Mutations in the **H-protein** gene (**GCSH**, **16q23.2**) = <1%

5. Nonketotic hyperglycinemia (NKH) or glycine encephalopathy

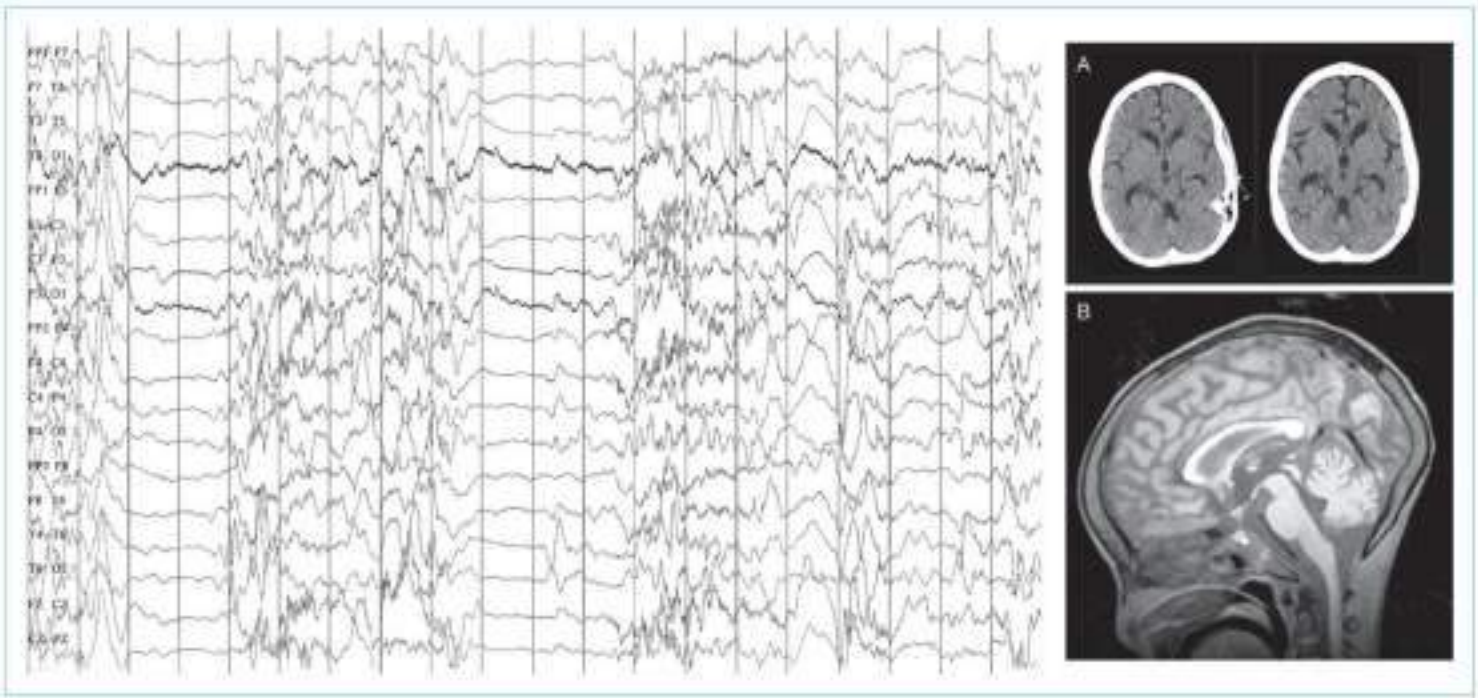
Presentation:

The onset is in **newborns**, who, within a few hours to days after birth become irritable with poor feeding and **hiccups**.
Subsequently, they develop a progressive encephalopathy with hypotonia, myoclonic seizures, and respiratory failure requiring mechanical ventilation.
Patients who survive the acute phase will have profound intellectual disability, spasticity, and intractable epilepsy.

Labs:
The diagnosis of glycine encephalopathy is established by detecting an **elevated CSF glycine concentration**, typically 15 to 30 times normal, in association with an increased ratio of CSF to plasma glycine (**normal < 0.02**).

Classic neonatal-onset patients often have ratios > 0.2
A ratio > **0.08 is usually considered diagnostic of glycine encephalopathy**.

EEG:



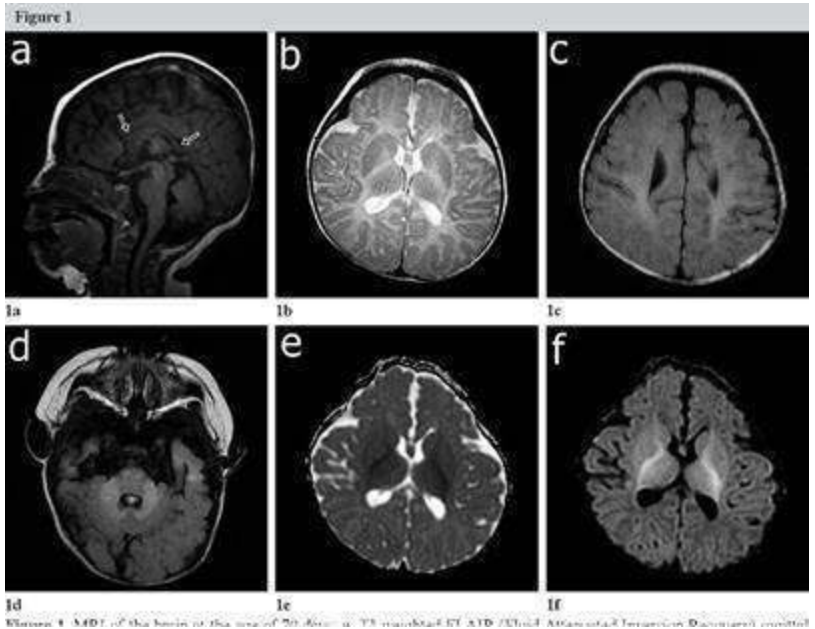
(A) CT scans performed at 8 years of age, 7 months apart, show progressive brain atrophy. (B) MRI done at 9 years of age shows diffuse brain atrophy and mild thinning of corpus callosum. EEG during sleep demonstrates a burst-suppression pattern.

5. Nonketotic hyperglycinemia (NKH) or glycine encephalopathy

EEG:
In the acute phase, the EEG shows **burst suppression and hypsarrhythmia.**

MRI:
May reveal a **hypoplastic or absent corpus callosum, gyral malformations, and cerebellar hypoplasia.**

<u>Normal MRI in 50% of neonates</u>



5. Nonketotic hyperglycinemia (NKH) or glycine encephalopathy

Treatment:

- No effective treatments are available
- **Sodium benzoate decreases plasma glycine concentrations**, but the CSF level does not normalize with this therapy, and neurologic dysfunction is not reversible.
- **Ketogenic diet** is reported to be a successful in glycine reduction and improving the overall outcome.
- **Benzodiazepines** can be used for seizures.
- **Dextromethorphan and ketamine** can be used to inhibit N-methyl-D-aspartate receptor excitation by glycine.
- **Valproate** is not advised.

6. Serine deficiency disorders

Serine deficiency disorders are caused by a defect in one of the three synthesising enzymes of the L-serine biosynthesis pathway.

A. 3-phosphoglycerate dehydrogenase (3-**PGDH**)
B. phosphoserine aminotransferase (**PSAT**)
C. phosphoserine phosphatase (**PSP**)

Presentation: infancy, GDD, microcephaly, cataract, spasticity, nystagmus, and refractory seizures.

Diagnosis: The diagnosis is based on the analysis of amino acids in the plasma and cerebrospinal fluid of the patient to detect serine deficiency and in some cases also glycine deficiency.

The enzymatic study allows for a differential diagnosis between the three synthesizing defects.

The genetic study confirms the defect and allows for genetic counseling and prenatal diagnosis.

Treatment: Administration of L- serine.

L-serine corrects not only the serine deficiency but also the glycine and folate deficiencies.

Patients that show a low concentration of plasma glycine can be treated with glycine and serine.

Supplementing with serine is very effective in the treatment of epileptic seizures.

6. Serine deficiency disorders

(A) Prenatal onset (Neu-Laxova syndrome):

- Severe intrauterine growth deficiency
- Microcephaly
- Congenital bilateral cataracts
- Dysmorphic features: sloping forehead, proptosis or short palpebral fissures with absent or abnormal eyelids, edematous and/or low-set or malformed ears, depressed nasal ridge, fixed narrow mouth with edematous lips, micrognathia, cleft palate, and short neck
- Thin, transparent, and tight skin with collodion-like ichthyosis
- Limb anomalies: short limbs, flexion contractures, cutaneous syndactyly, edematous hands and feet, rocker-bottom feet
- Neural tube defects
- MRI: cortical dysplasia with gyral simplification (anterior more than posterior), enlarged ventricles, decreased white matter, and structural abnormalities of the cerebellum

6. Serine deficiency disorders

(B) Infantile onset

- Intractable Seizures
- Microcephaly (congenital or postnatal)
- Developmental delay
- Severe intellectual disability
- Spastic quadriplegia Growth deficiency (prenatal and/or postnatal)
- Ocular: nystagmus, congenital bilateral cataracts, Ichthyosis
- MRI: Hypomyelination, white matter attenuation and delayed myelination, nonspecific cerebellar abnormalities

(C) Juvenile onset

- Seizures
- Developmental delay
- Intellectual disability
- Behavioral disorders
- Normal brain MRI

6. Serine deficiency disorders

Genetics:

AR, three genes (*PHGDH*, *PSAT1*, or *PSPH*)

Laboratory finding

- Cerebrospinal fluid (CSF) serine is very low, usually **<13 umol/L**, and in most individuals <10
- Fasting plasma **serine** is low, but non-fasting samples can be normal.
- CSF 5-methyltetrahydrofolate is very low
- CSF **glycine** is low to normal; fasting plasma glycine can be low to normal.
- Urine amino acids are noninformative; results are usually normal.

Treatment:

- L-serine therapy is started at 200-400 mg/kg/day to 500-700 mg/kg/day
- Glycine (200 mg/kg/day)

The Categories of IEM:

1. **Amino acid disorders (aminoacidopathies):** PKU, homocystinuria, MSUD, hartnup, NKH
2. **Organic acid disorders:** PA, MMA, IVA, MCD (biotinidase), glutaric aciduria 1
3. **Urea cycle defects:** OTC, CPS, NAGS, citrullinemia (ASSD), ASLD, ARG
4. **Disorders of carbohydrate metabolism:** Glucose (GSD), galactose (galactosemia), fructosemia
5. **Disorders of fatty acid & ketone body metabolism:** FAOD, carnitine d, glutaric acidemia II
6. **Disorders of energy substrate metabolism:** PCD
7. **Disorders of lipid metabolism:** X-linked adrenoleukodystrophy
8. **Disorders of lipoprotein metabolism:** HDL, LDL and/or triglycerides
9. **mtDNA-related disorders:** Single large-scale mtDNA deletions (Kearns–Sayre syndrome)
10. **Congenital disorders of glycosylation**: Type ! and II
11. **Disorders of complex molecule degradation:** Sphingolipid, GAG, glycoprotein, NCL, others
12. **Disorders of vitamin & cofactor metabolism:** Tetrahydrobiopterin, thiamine, pantothenate and CoA, pyridoxine, biotin, cobalamin, molybdenum cofactor.
13. **Disorders of trace elements & metals:** Copper, iron, zinc metabolism
14. **Disorders of nucleobase, nucleotide and nucleic acid metabolism:** Disorders of purine metabolism

II. ORGANIC ACID DISORDERS

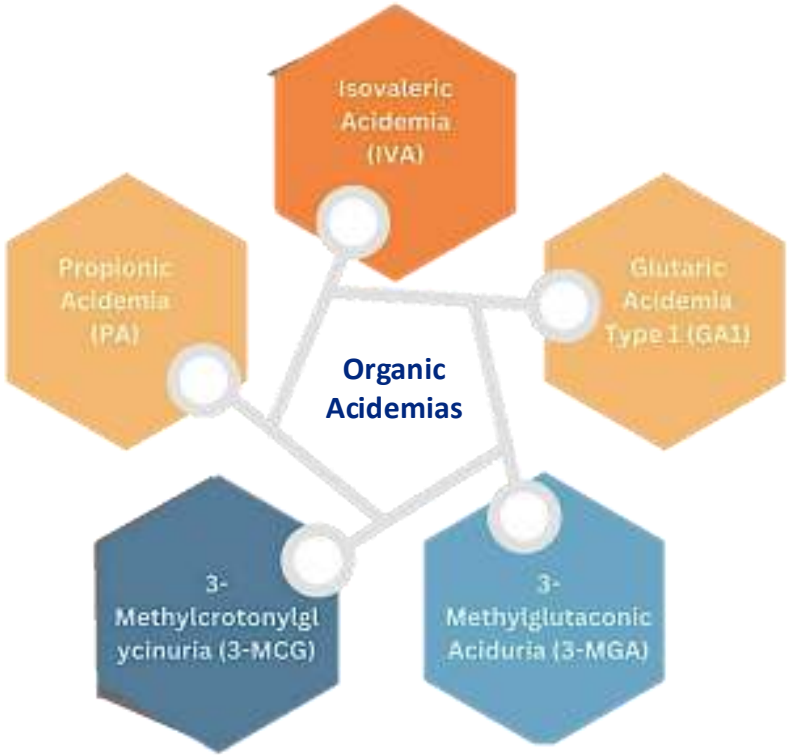
Deficiencies of enzymes (located in the mitochondria) needed for the metabolism of the activated carbon skeleton of amino acids.

Characterized by: Accumulation of organic acids proximal to the defective enzyme in the metabolic pathway.

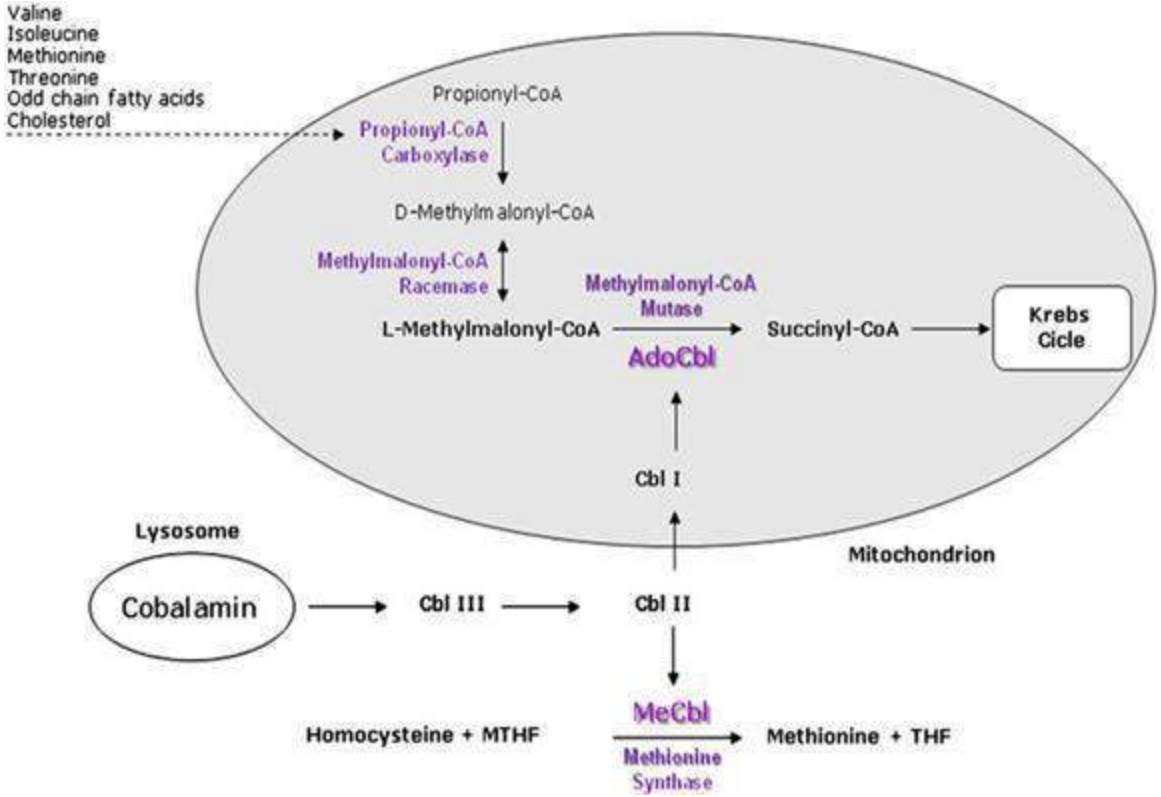
↑↑ **Organic acids = Deplete coenzyme A (CoA) + Impair urea cycle reactions -> HAGMA + Hyperammonemia -> Encephalopathy and seizures.**

↑↑ **Organic acids also have toxic effects on other organs (Bone marrow suppression, Cardiomyopathy, Renal dysfunction, and pancreatitis).**

II. ORGANIC ACID DISORDERS



II. ORGANIC ACID DISORDERS



II. ORGANIC ACID DISORDERS

Disorder	Abnormal metabolite(s)*
Organic acidemias	
Methylmalonic acidemia	Methylmalonic and methylcitric acids
Propionic acidemia	3-hydroxypropionic acid, propionylglycine, methylcitric acid
Isovaleric acidemia	Isovalerylglycine
Glutaric acidemia type I	Glutaric, 3-hydroxyglutaric, dicarboxylic acids, and acylglycine
3-methylglutaconic aciduria	3-methylglutaconic acid
2-hydroxy-3-methylbutyryl-CoA dehydrogenase deficiency	2-hydroxy-3-methylblutyric acid, tiglyglycine, 2-ethylhydracrylic acid
2-hydroxyglutaric aciduria	2-hydroxyglutaric acid

1. Propionic Acidemia

Definition:

OA caused by a deficiency of **propionyl-CoA carboxylase.** This enzyme normally participates in the carboxylation of **propionyl-CoA** to **D-methylmalonyl-CoA,** a step that requires the coenzyme **biotin**

MOA: AR, PA can result from mutations in PCCA or PCCB genes

Presentation:

- Children with propionic acidemia are normal at birth but develop symptoms either in the early neonatal period, in infancy, or later in childhood.
- **The classic presentation:** feeding difficulty, lethargy, hypotonia, dehydration, and attacks of metabolic acidosis and hyperammonemia
- They may progress to have seizures and coma.
- Hepatomegaly, pancytopenia, and bleeding disorders including intracranial hemorrhage are also other findings.
- Moderate hypocalcaemia and hyperlactataemia are frequently found

1. Propionic Acidemia

OA has ketotic hyperglycinemia while NKH has non-ketotic hyperglycinemia
Metabolic acidosis is usual presentation of OA, sometimes compensated by respiratory alkalosis which will confuse with UCA. to differentiate:
UCD has high glutamine while OA has normal glutamine

Diagnosis:

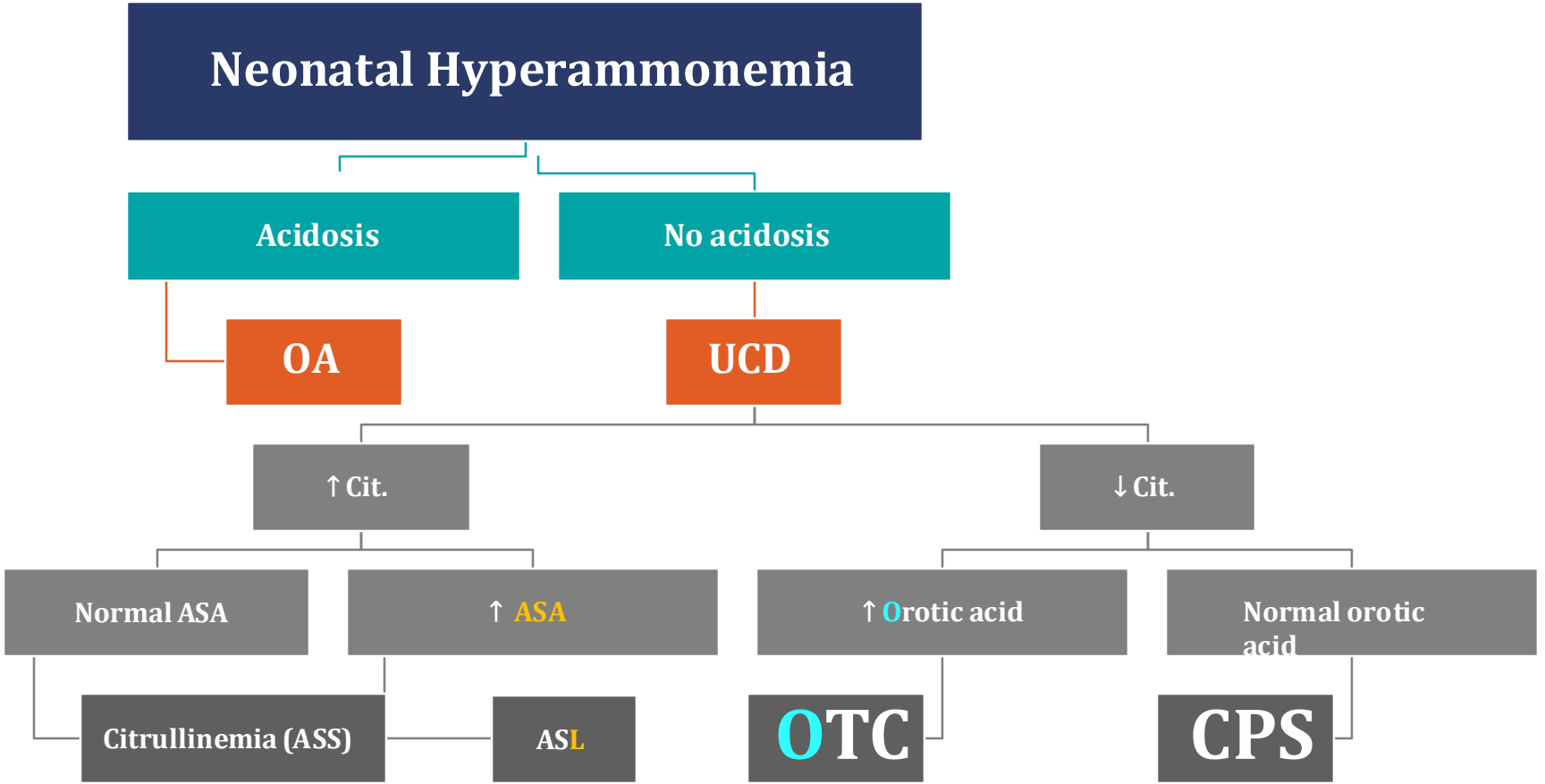
- Screened for by extended newborn screening
- Newborn babies with ketoacidosis, with an anion gap, and elevated propionic acid levels in the blood and sometimes in the urine
- Elevation of glycine levels in plasma and urine and of methylcitrate and B-hydroxypropionate in urine
- Enzyme activity in leukocytes or fibroblasts is reduced.

Treatment

- Restricted protein diet
- IV fluids for hydration
- Carnitine and biotin supplementation
- Dialysis may be required in some patients.
- Antibiotics such as metronidazole may decrease the production of propionate by enteric bacteria.

Prognosis

- Survivors have intellectual disability and basal ganglia abnormalities.



X-linked M/common M/sever

III. UREA CYCLE DEFECTS

These enzyme defects will lead to the **triad** of

1. hyperammonemia
2. encephalopathy
3. respiratory alkalosis the common clinical manifestations suggestive of this group of disorders.

Ammonia induces glutamine accumulation, which leads to astrocyte swelling and **brain edema**.

Clinical manifestations of OTC deficiency
Males often begin in the newborn period with **progressive lethargy, vomiting, hypotonia, and seizures.** Higher levels of ammonia may be associated with coma and eventually death.
Females with OTC deficiency, and some males with partial deficiencies, may have late-onset presentations and become symptomatic after large amounts of protein ingestion or intercurrent illnesses.
Arginase deficiency (ARG) does not cause symptoms in the newborn, whereas newborn presentation is common in the rest of urea cycle disorders.

III. UREA CYCLE DEFECTS

Clinical manifestation

1. **OTC deficiency**
   - **Males:** Newborn period with **progressive lethargy, vomiting, hypotonia, and seizures.** Higher levels of ammonia may be associated with coma and eventually death.
   - **Females** (+ some males) with partial deficiencies: Late-onset presentations and become symptomatic after large amounts of protein ingestion or intercurrent illnesses.
2. **Citrulimenemia:** ↑ blood citrulline

   Type I; with diminished levels of **ASS1** in all organs and type II or citrine deficiency.

   Type 2: transporter def, gene: **SLC25A13**.
3. **Argininosuccinic Aciduria:** ASL def, liver fibrosis and HTN, **Trichorrhexis nodosa**
4. **Arginase deficiency (ARG)** does not cause symptoms (encephalopathy) in the newborn, it causes progressive neurologic disorder (progressive spasticity (diplegia or quadriplegia).
5. **Hyperornithinemia-Hyperammonemia Homocitrullinuria Syndrome**

III. UREA CYCLE DEFECTS

Diagnosis

- High-serum ammonia, normal anion gap, and normal serum glucose level.
- Amino acid analyses help distinguish specific UCD and enzyme activity can be evaluated in liver biopsy.

Acute Treatment

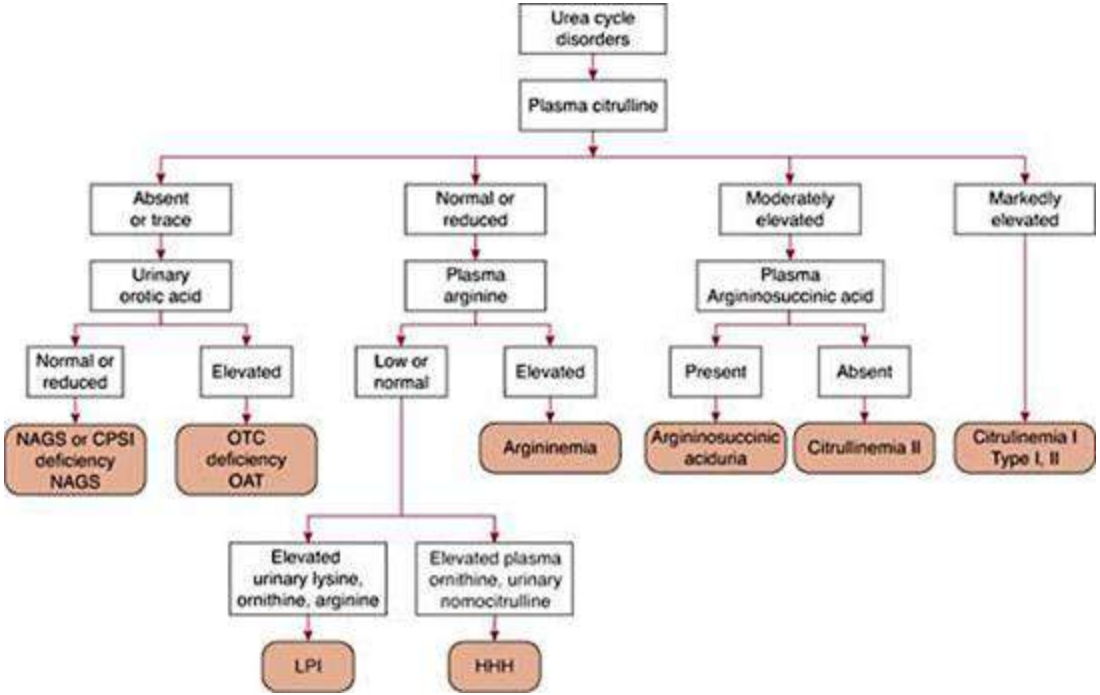
- **Limitation** of nitrogen intake in the diet
- **Essential amino acids.**
- **Calories** can be supplied with **carbohydrates and fat.**
- **Sodium benzoate and sodium phenylacetic acid**
- **Dialysis** may be required +/- **Mannitol** has been used for brain edema and increased intracranial **pressure.**

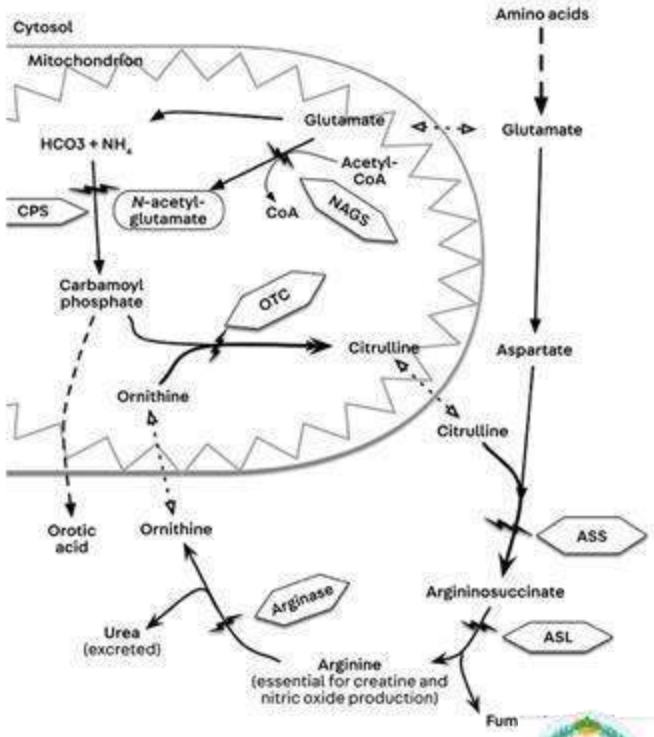
Long-term treatment

- Low- protein diet
- Essential amino acids
- Arginine supplementation (except in arginase deficiency), may stabilize the neurologic deterioration.

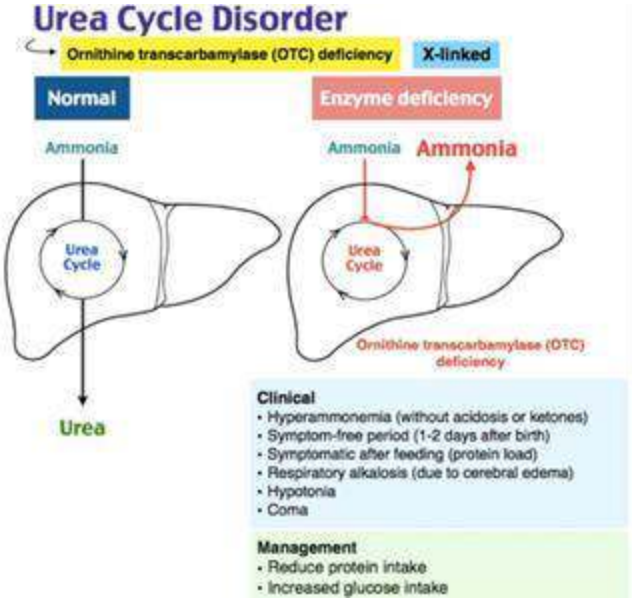
Definitive treatment -> Liver transplantation.

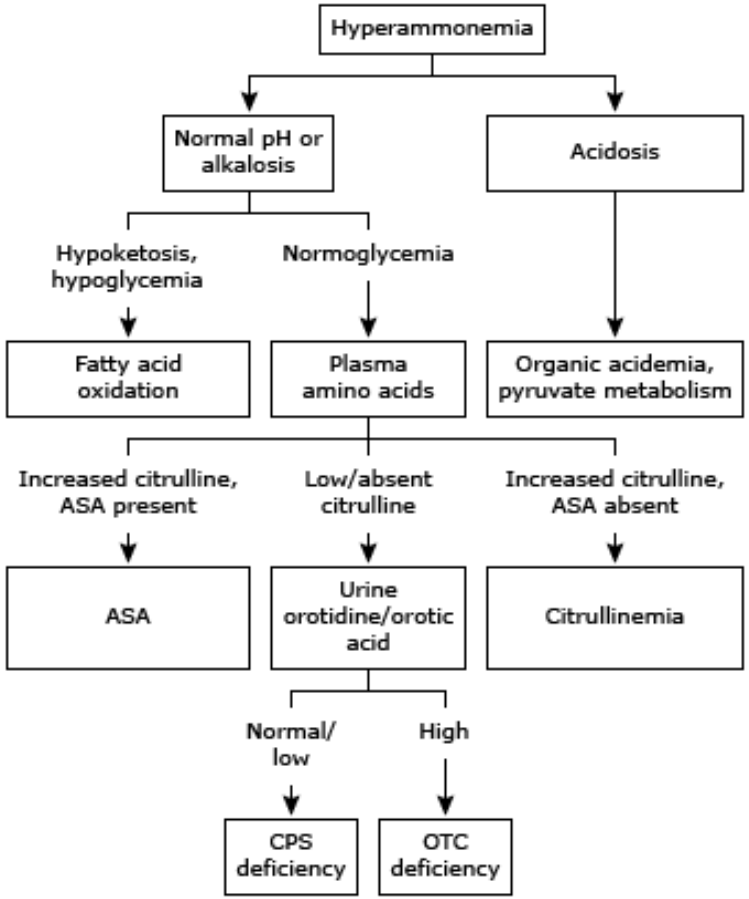
III. UREA CYCLE DEFECTS





III. UREA CYCLE DEFECTS





III. UREA CYCLE DEFECTS

Enzyme Deficiency	Urine Orotic Acid	Plasma Citrulline	Selected Clinical Characteristics
***N*-acetylglutamate synthase** (CASE 2-2)	Low	Low	Rarest of the urea cycle disorders; *N*-acetylglutamate synthase deficiency also has a specific and effective treatment, carglumic acid
Carbamoyl phosphate synthetase	Low	Low	Some patients with carbamoyl phosphate synthetase deficiency may also respond to carglumic acid
Ornithine transcarbamoylase (CASE 2-3)	High	Low	Most common urea cycle defects; X-linked; while often lethal in boys, girls who present in the neonatal period may do poorly as well; both men and women may present later in life with an episodic ataxia or encephalopathy, often associated with illness, high protein load, or steroid-triggered catabolism
Argininosuccinate synthetase	High	Very high	Presentation and management similar to ornithine transcarbamoylase deficiency
Argininosuccinate lyase	High	High, with high argininosuccinate	Episodic hyperammonemia; unique symptoms including hypertension, liver fibrosis, and developmental delay; plasma and CSF show elevated argininosuccinate
Arginase	High	Normal	Progressive spastic quadriplegia and mental retardation

Disorder	Inheritance	Enzyme or Transporter	Clinical Manifestations	Biochemical Markers	Diagnostic Tests
N-acetylglutamate synthase deficiency	Autosomal recessive	*N*-acetylglutamate synthase	Encephalopathy, neurobehavioral	Hyperammonemia, elevated plasma glutamine, low citrulline	DNA
Carbamyl phosphate synthetase deficiency	Autosomal recessive	Carbamyl phosphate synthetase	Encephalopathy, neurobehavioral	Hyperammonemia, elevated plasma glutamine, low citrulline	Liver enzyme analysis, DNA
Ornithine transcarbamylase (OTC) deficiency	X-linked semi-dominant	Ornithine transcarbamylase deficiency	Encephalopathy, neurobehavioral, liver disease (infrequently)	Hyperammonemia, elevated plasma glutamine, low citrulline, elevated urine orotic acid	DNA, liver enzyme analysis
Citrullinemia type I	Autosomal recessive	Argininosuccinate synthetase	Encephalopathy, neurobehavioral	Hyperammonemia, elevated plasma citrulline	Fibroblast enzyme analysis, DNA
Argininosuccinic aciduria	Autosomal recessive	Argininosuccinate lyase	Encephalopathy, neurobehavioral, liver disease (frequently), trichorrhexis nodosa	Hyperammonemia, elevated plasma citrulline, and argininosuccinic acid	Fibroblast enzyme analysis, DNA
Argininemia	Autosomal recessive	Arginase	Spastic diplegia, neurobehavioral	Elevated plasma arginine, elevated urine orotic acid	Red blood cell enzyme analysis
Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH)	Autosomal recessive	Ornithine mitochondrial transporter	Encephalopathy, neurobehavioral, spastic diplegia, retinal disease	Hyperammonemia, elevated plasma ornithine, elevated urine homocitrulline, elevated urine orotic acid	Fibroblast incorporation assay, DNA
Citrullinemia type II	Autosomal recessive	Citrin (aspartate/glutamate transporter)	Neuropsychiatric, neonatal cholestatic hepatitis	Hyperammonemia, elevated plasma citrulline, and arginine	DNA
Hyperdibasic aminoaciduria, (lysinuric protein intolerance)	Autosomal recessive	Dibasic amino acid transporter	Protein intolerance, vomiting, pulmonary alveolar proteinosis, glomerulonephritis, immune deficiency	Hyperammonemia, elevated urine lysine, ornithine, and arginine	DNA

TABLE 38-1 Long-Term Alternative-Pathway Treatment of Urea Cycle Disorders (UCDs)*

Disorder	L-Citrulline	L-Arginine Free Base	Sodium Phenylbutyrate	*N*-Carbamylglutamate
NAGS deficiency	—	—	—	~0.10 g/kg/d
CPS1 or OTC deficiency	0.15–0.20 g/kg/d or 3.8 g/m^2/d	—	0.45–0.60 g/kg if < 20 kg 9.9–13.0 g/m^2/d in larger patients	—
Citrullinemia	—	0.40–0.50 g/kg/d or 8.8–15.4 g/m^2/d	0.45–0.60 g/kg if < 20 kg 9.9–13.0 g/m^2/d in larger patients	—
Argininosuccinic acidemia	—	0.40–0.50 g/kg/d or 8.8–15.4 g/m^2/d	0.45–0.60 g/kg if < 20 kg 9.9–13.0 g/m^2/d in larger patients	—
Argininemia	—	—	0.45–0.60 g/kg/d if < 20 kg 9.9–13.0 g/m^2/d in larger patients	

*Drugs and dose ranges are those commonly used in patients with UCDs; however, doses can vary and need to be adjusted based on the severity of the disorder and patient response. When using doses at the upper recommended range or above, consideration should be given to increased risk of drug toxicity.

CPS1, carbamoyl-phosphate synthase 1; NAGS, *N*-acetylglutamate synthase; OTC, ornithine transcarbamylase.

Characteristic	Fructose-1,6-bisphosphate aldolase deficiency (HFI)	Fructose-1,6-diphosphatase (FDPase) deficiency
Enzyme Defect	Aldolase B deficiency - impaired cleavage of fructose-1-phosphate and fructose-1,6-bisphosphate	FDPase deficiency - impaired conversion of fructose-1,6-bisphosphate to fructose-6-phosphate
Primary Metabolic Block	Fructose-1-phosphate accumulation	Impaired gluconeogenesis
Biochemical Findings During Episodes	- ↑ Fructose-1-phosphate in liver and kidney - ↓ Inorganic phosphate in blood - ↑ Magnesium in blood - ↓ ATP in liver - ↑ Uric acid - Inhibition of gluconeogenesis and glycogenolysis - Normal lactate initially	- ↑ Fructose-1,6-bisphosphate - Severe lactic acidosis - ↑ Alanine - ↑ Ketones - ↑ Free fatty acids - ↑ Glycerol - ↑ Uric acid
Blood Tests During Crisis	- Hypoglycemia - Hypermagnesemia - Hypophosphatemia - Hyperuricemia - Elevated liver enzymes (ALT, AST) - Elevated bilirubin - Coagulopathy	- Hypoglycemia - Severe metabolic acidosis (pH < 7.2) - Increased anion gap - Elevated lactate (> 5 mmol/L) - Hyperuricemia - Normal liver function
Urine Findings	- Generalized aminoaciduria - Fructose (if recently ingested) - No significant organic acids	- Ketonuria - Increased lactate excretion - Glyceroluria
Diagnostic Tests	- Genetic testing (ALDOB gene) - Enzyme assay in liver tissue shows: • ↓ Fructose-1-phosphate aldolase activity • Normal fructose-1,6-bisphosphate aldolase activity	- Genetic testing (FBP1 gene) - Enzyme assay shows: • ↓ FDPase activity in liver • ↓ Activity in cultured lymphocytes
Specialized Tests	- IV fructose tolerance test (contraindicated): • ↓ Phosphate • ↑ Magnesium • No rise in blood lactate	- Glucagon stimulation test: • Minimal/no glucose response - Glycerol loading test: • Excessive lactate production
Post-Prandial Response to Fructose	- Rapid drop in phosphate and glucose - No significant lactate elevation - Accumulation of fructose-1-phosphate	- Normal fructose tolerance - No specific response to fructose intake
Fasting Response	- **Generally well tolerated** - Normal gluconeogenesis from non-fructose substrates	- **Rapid development of hypoglycemia** - Severe lactic acidosis - Impaired gluconeogenesis from all substrates

4. Glycogen storage disease (GSD)

GSD	Type 1 (Von Gierke)	Type 2 (Popme)	Type 3 (Cori)	Type 5 (McArdle)
Inheritance	AR			
Enzyme def.	Glucose 6-phosphatase	a-1.4 glucosidase	Amylo-1.6 glucosidase	Phosphorylase
Affected organs	Liver + kidney	All organs	Muscle + liver	Muscle
S&S	• Doll like facies • Short stature • Hepatomegaly • seizures • FTT • Ketotic hypoglycemia • Lactic acidosis • Hyperuricemia • Hyperlipidemia	• Cardioresp. Failure • Cause death before 2 yo	Like type 1 but milder course • Hepatomegaly • Hypoglycemia • Short stature • Skeletal myopathy • Cardiomyopathy	• Exercise intolerance cuz of painful muscle cramps • Burgundy colored urine after exercise (myoglobinuria 2ndry to rhabdomyolysis) • High CK , ammonia , uric acid

- **Hyperthermia under GA**
- **Subcutaneous fat deposition and xanthoma**

4. Glycogen storage disease (GSD) (Pompe disease)

In the infantile form, clinically significant storage occurs in the heart, resulting in **progressive cardiomegaly with left ventricular (LV) thickening that eventually leads to outflow tract obstruction**.

Storage in skeletal muscle leads to hypotonia and weakness.

The respiratory muscles are also affected, resulting in hypoventilation and progressive respiratory compromise.

hepatomegaly and macroglossia.

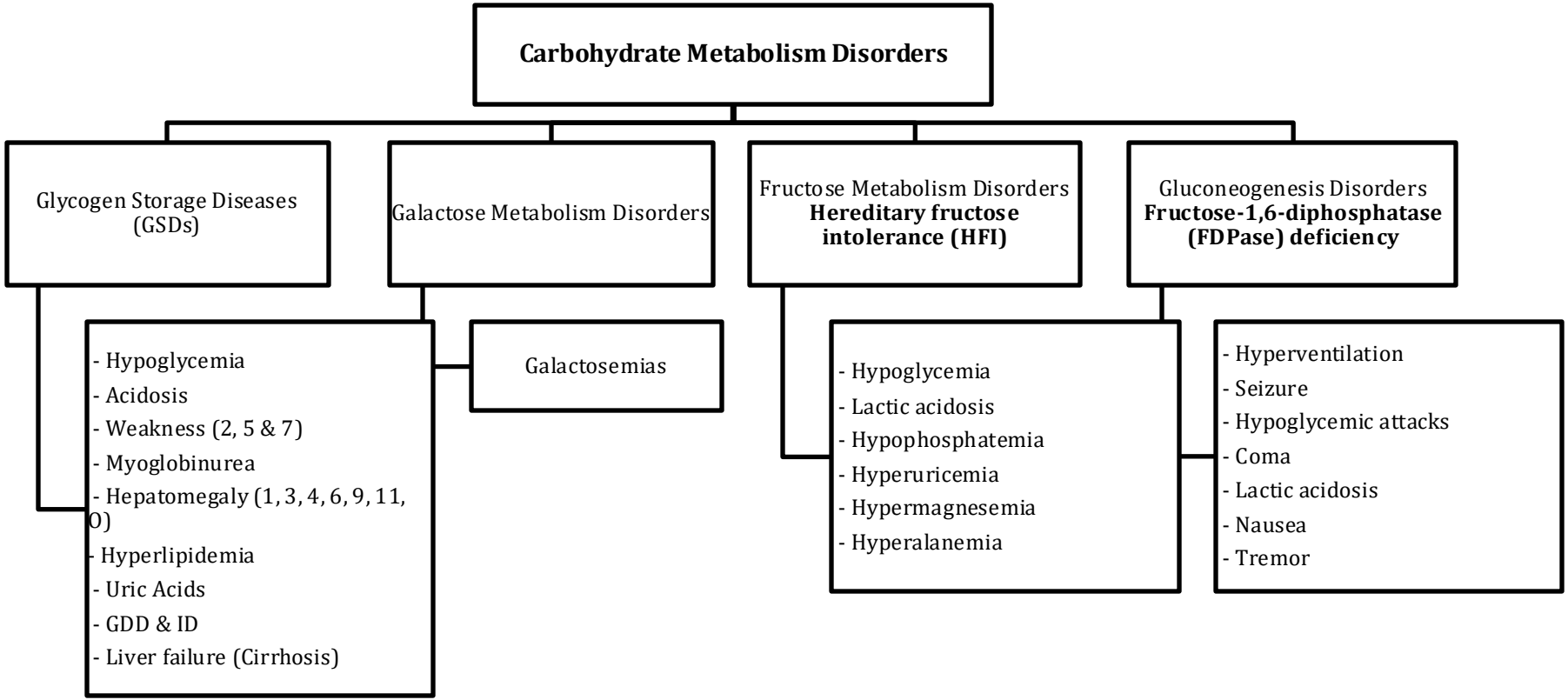
CNS involvement is primarily limited to the anterior horn cells of the spinal cord and brain stem nuclei, although intellectual performance remains normal. (SMA like symptoms)

Symptoms begin in the first months of life, with feeding problems, poor weight gain, muscle weakness, floppiness, and head lag.

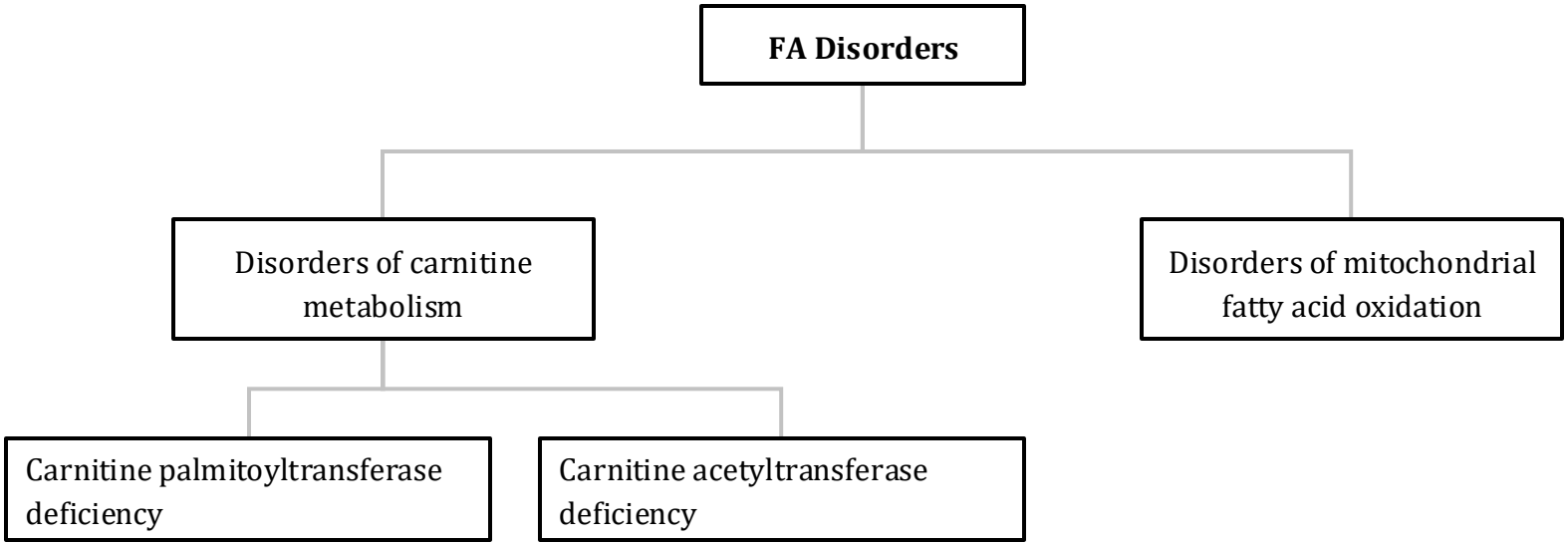
In late infantile form, Most have slowly progressive weakness but no cardiomegaly (DMD mimicker).

In Juvenile and adult, (LGMD mimicker) + fatigue

II. Carbohydrate metabolism disorders

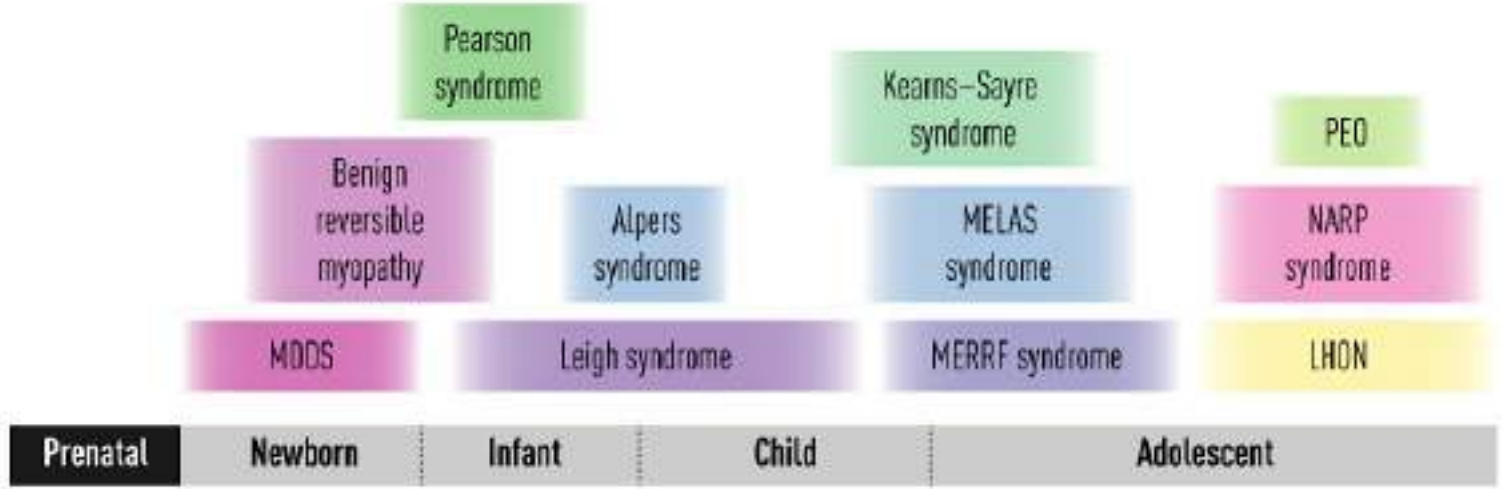


V. DISORDERS OF FATTY ACID & KETONE BODY METABOLISM



IX. mtDNA-related disorders

Mitochondrial defects:



Paediatric mitochondrial diseases arranged by age of onset. Canonical syndromic presentations of paediatric mitochondrial disease arranged according to age of onset.

Leber Hereditary Optic Neuropathy (LHON)

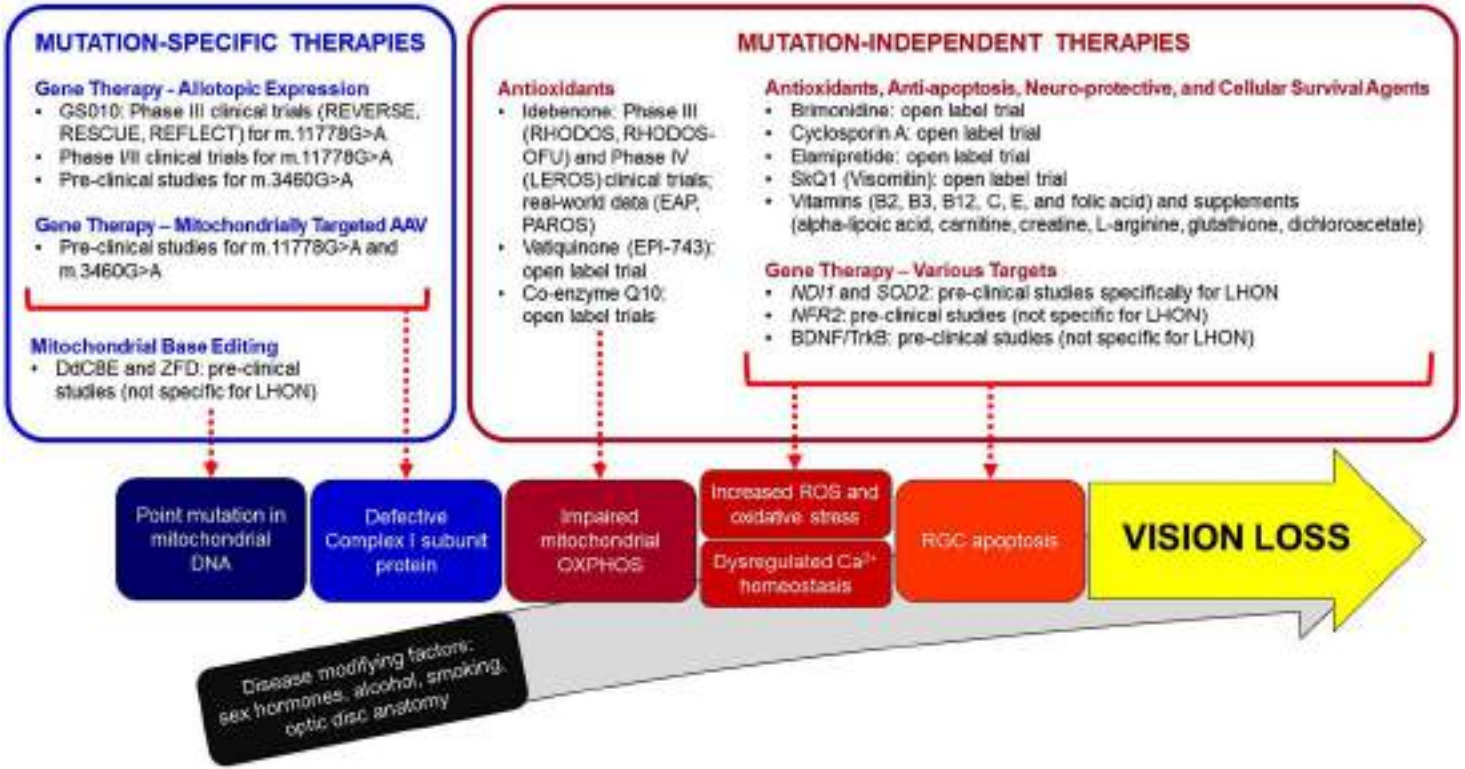
Diagnosis

- Clinical findings, especially if classic ophthalmologic features + Clear maternal history.
- Genetic testing remains the reference standard for confirming.

Treatment

Therapy	Description	Evidence	Reference
Idebenone	Synthetic analog of coenzyme Q10; enhances mitochondrial function	Improved VA in **RHODOS** trial; when initiated early	Klopstock et al., 2011 (Lancet)
Gene therapy (rAAV2/2-ND4)	Adeno-associated virus vector carrying the ND4 gene	Bilateral visual improvement in **REFLECT** study	Yu-Wai-Man et al., 2020
EPI-743	Para-benzoquinone analog; targets cellular redox balance	**Phase 2 trial** showed VA improvement.	Sadun et al., 2012
Supportive care	Low vision aids, occupational therapy, psychological support	Improves quality of life	Newman 2017
Risk factors	Smoking cessation	Observational studies	Kirkman 2009
Nutritional	Vitamins B2, B3, B12, C, E, and folate	Limited evidence	Pfeffer 2013

Leber Hereditary Optic Neuropathy (LHON) – Treatment

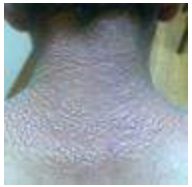


X. CONGENITAL DISORDERS OF GLYCOSYLATION

Pathway	Example disorders	Phenotype	Inheritance	OMIM	Key features by system								Diagnostic screen	Treatment
					Neurologic	Ophthalmologic	Cardiologic	Gastroenterological	Hematologic	Renal	Endocrine	Dermatologic	Musculoskeletal/other	
N-linked glycosylation	PMM2-CDG	CDG type Ia	AR	212065	ID (except MPI), DD, seizures (50%), hypotonia, ataxia, dysmetria, dysarthria, peripheral neuropathy, cerebral and cerebellar atrophy, myasthenia	Strabismus, nystagmus, optic hypoplasia, retinal pigmentary changes, alacrima	Pericardial effusion, cardiomyopathy, fetal hydrops	Protein losing enteropathy, diarrhea, FTT, GERD, hepatopathy with transaminitis, edema and hypoalbuminemia, low cholesterol	Coagulopathy and thrombosis (factor II, V, VII, VIII, IX, X, XI, antithrombin III, protein C, protein S deficiency), hypogammopathy	Hyperechoic kidneys, cysts, proteinuria	Thyroid abnormalities, IGF1 deficiency, hypogonadotropic hypogonadism, hyperinsulemic hypoglycemia	Lipodystrophy, hypohidrosis	Osteopenia, kyphoscoliosis, dysmorphic features, skeletal dysplasia, SS	Transferrin profiling, urine oligosaccharide analysis	–
	MPI-CDG	CDG type Ib	AR	602579										Mannose 1 g/kg/day, div 4-6 doses
	ALG6-CDG	CDG type Ic	AR	603147										–
O-linked glycosylation	EXT1/EXT2-CDG	Multiple exostoses type I/II	AD	133700, 133701	ID (most), DD, muscular dystrophy, hypotonia, polymicrogyria, lissencephaly	Structural eye abnormalities, glaucoma, isolated macular corneal dystrophy, corneal opacity, cataracts	–	FTT	–	–	Tumoral calcinosis with phosphatemia	Loose skin, reticulate pattern of hyperpigmentation	Skeletal dysplasia, SS, hypermobility, exostoses, elevated CK, dysmorphic features	–	–
	B3GLCT-CDG	Peters-plus syndrome	AR	261540											–
	GALNT3-CDG	Hyperphosphatemic familial tumoral calcinosis	AR	211900											–
	SLC35C1-CDG	Leukocyte adhesion deficiency type II	AR	266265											Fucose
Mixed glycosylation	TMEM165-CDG	CDG type IIk	AR	614727	Seizures, ID (not universal), DD, microcephaly, hypotonia, cortical and cerebellar atrophy	All findings seen in N-linked pathway possible	Cardiomyopathy, congenital structural heart defects	All findings seen in N-linked pathway possible, isolated polycystic liver disease, high cholesterol, cholestatic liver disease, IUGR	Isolated leukocyte adhesion deficiency, isolated congenital dyserythropoietic anemia type II, immunodeficiency	Obstructive uropathy, micropenis, hypospadias	–	Ichthyosis, cutis laxa, hypohidrosis	Skeletal dysplasia, dysmorphic features, elevated CK	Transferrin profiling with APO-CIII profiling	Galactose 1.5–2.5 g/kg/day (max 50 g) for endocrinopathy and coagulopathy
GPI anchor disorder	PIGA-CDG	PIGA deficiency	XL	300868	Seizures, ID, DD, macrocephaly, hypotonia	–	Congenital heart defects, cardiomyopathy	–	–	–	Accelerated linear growth, advanced bone age, +/− hyperphosphatasia	–	Dysmorphic features, multiple congenital anomalies	Flow cytometry studies using cell surface markers like FLAER and CD59 on granulocytes, lymphocytes, etc.	Ketogenic diet for seizures
	PIGM-CDG	PIGM deficiency	AR	610293											Sodium butyrate for seizures
Lipid glycosylation	ST3GAL5-CDG	Amish infantile epilepsy syndrome	AR	609056	Seizures, ID, DD, hypotonia, diffuse brain atrophy, irritability, microcephaly	Optic atrophy, cortical visual impairment	–	FTT	–	–	–	Dyspigmentation, "salt and pepper" pattern on skin macules, skin hyperextensibility	Progeroid appearance, joint laxity	–	–
	B4GALNT1-CDG	Spastic paraplegia 26	AR	609195											

AR, autosomal recessive; AD, autosomal dominant; XL, X-linked; ID, intellectual disability; DD, developmental delay; FTT, failure to thrive; GERD, gastro-esophageal reflux; IUGR, intrauterine growth restriction; SS, short stature; CK, creatine kinase; OMIM, Online Mendelian Inheritance in Man; MPI, mannose phosphate isomerase; CDG, congenital disorders of glycosylation.

III. Mucopolysaccharidosis (MPS):

Dis	**MPS I**	**MPS II**	**MPS III**	**MPS IV**	**MPS VI**	**MPS VII**
	Hurler (AR)	*Hunter (XLR)*	*Sanfilippo (AR)*	*Morquio (AR)*	*Maroteaux Lamy*	*Sly syndrome*
Enzy + Gene	**Alpha L Iduronidase** enzyme, Gene Iduronidase, alpha-L (IDUA), Ch 4 **TTT: ERT + SCT**	**Iduoronate sulfate sulfatase** **TTT: ERT**	**A**: Heparan S sulfamidase **B:** Alpha N acetylglucosaminidase **C**: Acetyl-CoA: alpha glucosaminide n-acetyl transferase **D:** N acetylglucosamine 6 sulfatase	**A:** Galactosamine 6 sulfatase **B:** Beta galactosidase	Arylsulfatase B	B-Gluconidase
Acc	**Dermatan + Heparan**	**Dermatan + Heparan** sulfate	**Heparan sulfate** only	Keratan Sulphate	dermatan sulphate	
Clinical	**H (Severe):** HSM, breathing difficulties, dysostosis, heart disease, hearing, **hydrocephalus**, myelopathy, and coarse face **HS**: Micrognathia, toe walking, coarse face **S:** Least severe **(normal IQ)**	- **Mild or no ID** - **No corneal clouding** - **Nodular ivory-colored lesions** - short stature - macrocephaly - macroglossia - hoarse voice - hearing loss - visceromegaly - dysostosis multiplex - joint contractures - entrapment neuropathies (CTS) 	**- Intellectual disability** **- Aggression** - behavioral problems - developmental delay - sleep disorders	- **Normal IQ** - **Short** stature - **Lax** ligaments - Genu valgum - C1-2 subluxation - Hearing loss - Coarse face - Heart disease	- **Normal IQ** **- Spinal cord compression** - Dysostosis multiplex - Corneal clouding - Heart disease - Hurler like	**- Hydrops fetalis** - Intellectual disability - Dysostosis multiplex - Hurler like

III. Mucopolysaccharidosis (MPS):

MANIFESTATIONS	MUCOPOLYSACCHARIDOSIS TYPE						
	I-H	I-S	II	III	IV	VI	VII
Mental deficiency	+	−	±	+	−	−	±
Coarse facial features	+	(+)	+	+	−	+	±
Corneal clouding	+	+	−	−	(+)	+	±
Visceromegaly	+	(+)	+	(+)	−	+	+
Short stature	+	(+)	+	−	+	+	+
Joint contractures	+	+	+	−	−	+	+
Dysostosis multiplex	+	(+)	+	(+)	+	+	+
Leucocyte inclusions	+	(+)	+	+	−	+	+
Mucopolysaccharidurla	+	+	+	+	+	+	+

I-H, Hurler disease; I-S, Scheie disease; II, Hunter disease; III, Sanfilippo disease; IV, Morquio disease; VI, Maroteaux-Lamy disease; VII, Sly disease.

MPS TYPE	EPONYM	GENE Inheritance	GENE Chromosome	MAIN CLINICAL FEATURES	DEFECTIVE ENZYME	ASSAY	MIM NUMBER
I-H	Pfaundler-Hurler	AR	*IDA* 4p16.3	Severe Hurler phenotype, mental deficiency, corneal clouding, death usually before age 14 yr	α-L-Iduronidase	L,F,Ac,Cv	252800 607014
I-S	Scheie	AR	*IDA* 4p16.4	Stiff joints, corneal clouding, aortic valve disease, normal intelligence, survive to adulthood	α-L-Iduronidase	L,F,Ac,Cv	607016
I-HS	Hurler-Scheie	AR	*IDA* 4p16.4	Pheotype intermediate between I-H and I-S	α-L-Iduronidase	L,F,Ac,Cv	607015
II	Hunter	XLR	*IDS* Xq27.3-28	Severe course similar to I-H but clear corneas. Mild course: less pronounced features, later manifestation, survival to adulthood with mild or no mental deficiency	Iduronate sulfate sulfatase	S,F,Af,Ac,Cv	309900
III-A	Sanfilippo A	AR	*HSS* 17q25.3	Behavioral problems, sleeping disorder, aggression, progressive dementia, mild dysmorphism, coarse hair, clear corneas, survival to adulthood possible	Heparan-S-sulfamidase	L,F,Ac,Cv	252900 605270
III-B	Sanfilippo B	AR	*NAGLU* 17q21		N-Ac-α-glucosaminidase	S,F,Ac,Cv	252920
III-C	Sanfilippo C	AR	*HGSNAT* *8p11-q13*		Ac-CoA-glucosaminide-N-acetyltransferase	F,Ac	252930
III-D	Sanfilippo D	AR	*GNS* 12q14		N-Ac-glucosaminine-6-sulfate sulfatase	F,Ac	252940 607664
IV-A	Morquio A	AR	*GALNS* 16q24.3	Short-trunk dwarfism, fine corneal opacities, characteristic bone dysplasia; final height <125 cm	N-Ac-galactosamine-6-sulfate sulfatase	L,F,Ac	253000
IV-B	Morquio B	AR	*GLB1* 3p21.33	Same as IV-A, but milder; adult height >120 cm	β-Galactosidase	L,F,Ac,Cv	253010 230500
VI	Maroteaux-Lamy	AR	*ARSB* 5q11-q13	Hurler phenotype with marked corneal clouding but normal intelligence; mild, moderate, and severe expression in different families	N-Ac-galactos-amine-α-4-sulfata sulfatase (arylsulfatase B)	L,F,Ac	253200
VII	Sly	AR	*GUSB* 7q21.11	Varying from fetal hydrops to mild dysmorphism; dense inclusions in granulocytes	β-Glucuronidase	S,F,Ac,Cv	253220
IX	Hyaluronidase deficiency	AR	*HYAL1* 3p21.3	Periarticular masses, no Hurler phenotype	Hyaluronidase 1	S	601492

Ac, cultured amniotic cells; Af, amniotic fluid; Cv, chorionic villi; F, cultured fibroblasts; L, leukocytes; MIM, Mendelian Inheritance in Man Catalog; S, serum.

III. Mucopolysaccharidosis (MPS):

Table 39.1 The 7 different MPS, with the most important clinical signs and symptoms

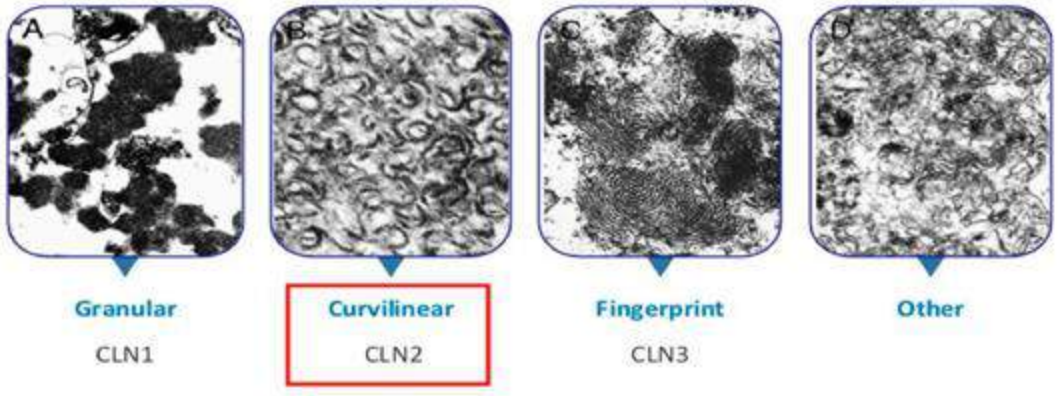
MPS Type	Disease name	Dysostosis multiplex	Valvular heart disease	Progressive cognitive impairment	Spinal cord compression
MPS IH	Hurler	+++	+++	+++	++
MPS IH-S	Hurler-Scheie	++	++	++	++
MPS IS	Scheie	++	++	-	++
MPS II	Hunter, neurono-pathic phenotype	++	++	+++	++
	Hunter, attenuated phenotype	++	++	-/+	++
MPS IIIA	Sanfilippo A	+	+/-	+++	-
MPS IIIB	Sanfilippo B	+	+/-	+++	-
MPS IIIC	Sanfilippo C	+	+/-	+++	-
MPS IIID	Sanfilippo D	?	?	+++	-
MPS IVA	Morquio A	+++	+	-	+++
MPS IVB	Morquio B	+++	+	-	+++
MPS VI	Maroteaux-Lamy	+++	+++	-	+++
MPS VII	Sly	+++	++	+++	+
MPS IX	-	?	?	?	?
Multiple sulfatase deficiency	Austin	++	+	+++	?

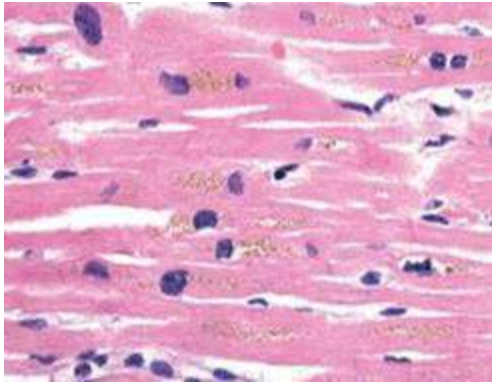
Accumulating GAGs: *HS*, heparan sulfate; *DS*, dermatan sulfate; *KS*, keratan sulfate; *CS*, chondroitin sulfa
Presence of signs and symptoms: -: never reported; +/-: vary rare; +: can be present; ++: often present; +

IV. Neuronal ceroid lipofuscinosis (NCL):

Neuronal Ceroid Lipofuscinoses NCL (batten disease)

- Heterogeneous group of neurodegenerative disorders, characterized by the intracellular storage of certain lipo-pigments (lipofuscin, an autofluorescent 'wear-and-tear pigment)
- Its group of lysosomal storage disorder
- WE have 4 types of lipopigments under electronic microscope
- Fingerprint
- Curvilinear
- Granular osmiophilic deposits (grods)
- Rectilinear





Yellow-brown (granular intracytoplasmic, often perinuclear)pigment

IV. Neuronal ceroid lipofuscinosis (NCL):

All NCL types share:

1-Autofluorescent, electron-dense, periodic acid- Schiff (PAS) and Sudan black B-positive granules lipofusenosis

2-Progressive and selective loss of neurons, particularly in the cerebral and cerebellar cortex and, less constantly, in the retina, leading to cognitive, motor and visual deterioration with refractory epilepsy

ALL CLN are AR except CLN 4b is AD

- 360 mutations in 13 different genes
- 10–12% of patients affected with a progressive neurological disorder, whose clinical and neurophysiological features are consistent with a diagnosis of NCL, the gene mutations remain undefined

Intracellular localization and function (where known) of the defective proteins are different:

1. Defect lysosomal enzymes (CLN1, CLN2, CLN10, CLN13),
2. Defect in transmembrane proteins (CLN3, CLN6, CLN7, CLN8)
3. Mutations in an ATPase gene (CLN12)
4. Mutation potassium channel gene (CLN14).

**** The only form of NCL that is treatable is NCL2, Cerliponase Alfa**

Name	Age	Gene	Clinical					Others	Investigation	Biopsy
			HC	Motor	Development	Seizure	Visual			
NCL1	3-18 m Infantile	PPT1	Progressive microcephaly	Hypotonic then spastic tetraplegia	Delay	Myoclonus then other form of generalized seizure	Rapid visual loss	Irritability Automatism	EEG: Occipital attenuation with eye closure and opening leading to an isoelectric tracing ('vanishing EEG') Brain MRI: severe atrophy	Granular osmiophilic deposits (**GROD**)
NCL2	2-3 y Late infantile	TPP1	-	Hypotonic & ataxic > bed bounded	Regression	Myoclonus, atypical absence seizure, LGS	Late Rapid decline (macular degenration)		Low frequency (1-3 Hz) photic stimulation causes a posterior spike response	Curvilinear
NCL3	4-9 y	CLN3B	-	Pyramidal, Extrapyramidal Cerebellar signs	Regression Behavioral change Self-mutilation	Myoclonic then other forms	Decline pigmented retina (hemeralopia, day blindness)	Cardiac conduction	CT Extensive calcification	Fingerprints
NCL5	4-5 y	CLN5	-	4. ataxia	-	3. myoclonic jerks	2. decline in vision	1. learning difficulties	-	Fingerprints and Curvilinear
NCL6	4-5 y	CLN6	-	2. Ataxia	Motor regression	3.Myoclonic and other seizure form	4. visual decline	-	-	Fingerprints and Curvilinear
NCL7	Late infantile	CLN7	-	-	-	-	-	-	-	Fingerprints and Curvilinear
NCL8	Early & late infancy	R24G/ CLN8	Two different types: 1. Progressive epilepsy with mental retardation, or northern epilepsy 2. Turkish late infantile variant							Fingerprints and Curvilinear
NCL10	Birth/Cong	CTSD	Microcephaly	Lack of development	No development	-	-	Early Death	-	-

**** The only form of NCL that is treatable is NCL2, Cerliponase Alfa**

IV. Neuronal ceroid lipofuscinosis (NCL):

** The only form of NCL that is treatable is NCL2, Cerliponase Alfa

1. Developmental delay/regression
2. Visual loss
3. Myoclonic jerks

TABLE 1 | NCL of childhood onset: clinical classification and major diagnostic procedure.

Clinical form	Age of onset	Disease	Gene	Diagnosis	Major symptoms at onset
Congenital	Birth	CLN10	*CLN10/CTSD*	NGS Enzymatic assay	Microcephaly, dysmorphic features, seizures, hyperkinetic movements;
Infantile	6–18 months	CLN1	*CLN1/PPT1*	NGS enzymatic assay	Decreased head growth, neuro-developmental regression, seizures;
		CLN10	*CLN10/CTSD*	NGS enzymatic assay	Decreased head growth, neuro-developmental regression;
		CLN14	*CLN14/KCDT7*	NGS	Decreased head growth, seizures (myoclonus);
Late infantile					
Classical	2–4 yrs	CLN2	*TPP1*	NGS enzymatic assay	Seizures, ataxia, visual loss, delayed language development;
Variant	2–5 yrs	CLN1	*CLN1/PPT1*	NGS enzymatic assay	Seizures, neuro-developmental regression, behavioral disturbances;
		CLN5	*CLN5*	NGS	Impaired learning and cognition;
		CLN6	*CLN6*	NGS	Seizures, ataxia, delayed language development;
		CLN7	*CLN7/MFSD8*	NGS	Seizures, visual loss, motor and cognitive regression;
		CLN8	*CLN8*	NGS	Seizures, visual loss, motor and cognitive regression;
Juvenile					
Classical	3–5 yrs	CLN3	*CLN3*	NGS	Visual loss, behavioral problems, cognitive decline
	5–7 yrs	CLN5	*CLN5*	NGS	Motor and cognitive regression, behavioral problems;
	5–7 yrs	CLN1	*CLN1/PPT1*	NGS enzymatic assay	Visual loss, cognitive decline;
Late	8–12 yrs	CLN6 CLN10	*CLN6* *CLN10/CTSD*	NGS NGS enzymatic assay	Myoclonic seizures, cognitive decline; ataxia, cognitive decline, visual loss;
	13–16 yrs	CLN12	*ATP13A2*	NGS	Rigidity, hypokinesia

IV. Neuronal ceroid lipofuscinosis (NCL):

1. **Developmental delay/regression**
2. **Visual loss**
3. **Myoclonic jerks**

**** The only form of NCL that is treatable is NCL2, Cerliponase Alfa**

TABLE 4 | Selected therapeutic trials (completed and on-going).

Disease	Therapy	Study	Via	Vector/Product	Clinical trial code#
CLN2	ERT* cerliponase alpha (Brineura)	Phase 1/2 open label Safety and efficacy	i.c.v.	Recombinant protein	NCT01907087
CLN2	ERT*	Open label Long term efficacy	i.c.v.	Recombinant protein	NCT02485899
CLN2	GRT*	Safety	i.c.	AAVrh.10CUhCLN2	NCT01161576
CLN3	GRT	Phase 1/2 open-label	i.t.	AT-GTX-502	NCT03770572
CLN6	GRT	Phase 1/2 open-label	i.t.	AT-GTX-501	NCT02725580
CLN6	GRT	Long term efficacy	None	AT-GTX-501-01	NCT04273243
CLN7	GRT	Phase 1 open-label	i.t.	AAV9/CLN7	NCT04737460
CLN3	SRT	Phase 1/2	os	BBDF 101	None

*ERT, Enzyme Replacement Therapy; GRT, Gene Replacement Therapy; SRT, Substrate Reduction Therapy; i.c.v., intracerebralventricular injection; i.c., intracerebral (burr holes) injection; i.t., intrathecal injection. *completed studies. #ClinicalTrials.gov.*

CLN1 = PPT1 INFANT
CLN2 = TPP1 OR TTP1 = LATE INFANT
CLN10 = NEONATE OR ADULT DNAJCS OR CSP
CLN8 = LATE INFANT
CLN4,6 = INFANT / ADULTS

V. Mucolipidosis:

Mucolipidosis when originally named, they derived their name from the similarity in presentation to both mucopolysaccharidoses and sphingolipidoses.

A biochemical understanding of these conditions has changed how they are classified.

Four conditions (types I, II, III, and IV) were historically labeled as mucolipidoses.

However, type I (sialidosis) is now classified as a glycoproteinosis, and type IV (Mucolipidosis type IV) is now classified as a gangliosidosis

Table 9.2 The Mucolipidoses (ML) and Sialidoses

Type	Age at onset	Clinical features	Enzyme deficiency (gene location)
Sialidosis I (cherry-red spot–myoclonus syndrome)	Late childhood to adulthood	Action and intention myoclonus, retinal cherry-red spot, normal intelligence, no dysmorphism	Sialidase (alpha-neuraminidase) (6p21)
Sialidosis II or ML II	Congenital to second decade	Facial dysmorphism, gingival hyperplasia, hepatosplenomegaly, severe intellectual disablity, macular cherry red spot, renal failure	Sialidase (alpha-neuraminidase) (6p21)
ML II (I-cell disease)	First year of life	Dysmorphism, gingival hyperplasia, severe neurodevelopmental deterioration	N-acetylglucosamine-1-phosphotransferase (12q23.3)[a]
ML III (pseudo-Hurler polydystrophy)	Early childhood	Moderate intellectual disability in 50% of cases, Hurler-like or Morquio-like skeletal dysplasia	N-acetylglucosamine-1-phosphotransferase (12q23.3)[a]
ML IV	Early childhood but may be later, even into adulthood (male form)	Severe intellectual disability corneal clouding, no bony or visceral involvement, self-mutilation	Mucolipin I (MCOLN1 at 19p13.2–13.3) Casteels et al. (1992), Bach (2001), Slaugenhaupt (2002)
ML V	Late childhood	Dysostosis multiplex, hepatosplenomegaly	Dysostosis multiplex, hepatosplenomegaly Cathepsyn K, (CTSK) gene

Sialic acid is increased in urine

CLINICAL CLUES

Radiological

X-ray		Neuroimaging		Others	
Dysostosis Multiplex	LSD	**White matter changes**	LSD, Peroxisomal, Mitochondrial, OA, TBRBGD	**Nephromegaly or renal cyst**	Peroxisomal
Punctate calcification	Peroxisomal	**Brain malformations**	Peroxisomal, molybdenum	**Cardiomyopathy**	LSD, Mitochondrial, OA, GSD
Rhizomelic shortening	Peroxisomal	**Cystic changes**	Molybdenum, Pyruvate		
Erlenmeyer flask deformity	LSD				

CLINICAL CLUES

MRI

Disorder	Classification	Defect + Metabolic Consequence	Key MRS Metabolite (ppm) or MRI Feature
Maple syrup urine disease (MSUD) *	Amino aciduria	Defect in branched-chain keto-acid dehydrogenase enzyme → ↑ branched chain amino acids and ketoacids (BCAAs, BCKAs)	↑ BCAAs + BCKAs (0.9) Intramyelinic edema involving cerebrum, cerebellum, brainstem
Non-ketotic hyperglycinemia (NKH) *	Amino aciduria	Defective mitochondrial enzyme involved in glycine cleavage → ↑ glycine	↑ Glycine (3.5) Intramyelinic edema, Hypogenesis corpus callosum, vermian hypoplasia
Phenylketonuria (PKU) *	Amino aciduria	Phenylalanine hydroxylase deficiency	↑ Phenylalanine (7.37) Periventricular and subcortical white matter (WM) abnormalities
Glutaric Aciduria type I (GA-I) *	Organic aciduria	Enzyme deficiency altering lysine, hydroxylysine, tryptophan metabolism→ ↑ glutaric acid, hypoglycemia	Poorly formed operculum, widened sylvian fissures and frontotemporal subarachnoid spaces, basal ganglia (BG) lesions
L-2-hydroxyglutaric aciduria (L2HGA) *	Organic aciduria	Mitochondrial enzyme L2HGDH mutation→ ↑ L-2-hydroxyglutaric acid	Initial frontal and subcortical WM, with later confluent WM and BG abnormality. Dentate nuclei lesions

CLINICAL CLUES

MRI

Methylmalonic acidemia (MMA)	Organic aciduria	Defect in methylmalonyl-coenzyme A mutase→ ↑ methylmalonic acid, glycine, ammonia	Cerebral WM and globus pallidus lesions
Propionic acidemia	Organic aciduria	Defect in propionyl-coenzyme A carboxylase	↑ propionic acid, glycine Cerebral WM and striatum lesions
Urea cycle defects (UCD)	Urea cycle defects (UCD)	Deficiency in detoxification of ammonia to urea→ ↑ ammonia, glutamine	↑ Glu ± ↓ mI and Cho Cortical and subcortical lesions usually sparing thalamus
α-Mannosidosis *	Lysosomal	Deficiency of α-mannosidase	Mannose-rich oligosaccharides (3.5–3.9) Hypomyelination Leukodystrophy (LD)
Fucosidosis *	Lysosomal	Deficiency of α-L-fucosidase needed to metabolize fucose-containing compounds	Carbohydrate-containing macromolecules (3.8–3.9) Fructose (1.2 doublet); inverts at intermediate echo time Hypomyelination, thalamic and GP T2 hypointensity
Globoid cell leukodystrophy (Krabbe disease)	Lysosomal	Galactocerebroside β-galactosidase deficiency → globoid cell accumulation	Thalamic T2 hypointensity Centrifugal gradient LD, tigroid WM pattern, cranial nerve enhancement, optic nerve enlargement

CLINICAL CLUES

MRI

Disorder	Classification	Defect + Metabolic Consequence	Key MRS Metabolite (ppm) or MRI Feature
Metachromatic leukodystrophy (MLD)	Lysosomal	Decreased arylsulfatase A enzyme activity → metachromatic sulfatide deposits	Centrifugal gradient LD, tigroid WM pattern, cranial nerve enhancement
Mucopolysaccharidosis (MPS) *	Lysosomal	Deficiencies in lysosomal hydrolases responsible for metabolizing mucopolysaccharides (a.k.a. glycosaminoglycans)	Mucopolysaccharides (3.6–3.7) ↑ Cho Enlarged perivascular spaces, ventriculomegaly, WM lesions, dysostosis multiplex, CVJ stenosis
Salla disease *	Lysosomal	Defect in sialic acid transport → N-acetyl neuraminic acid	↑ N-acetyl neuraminic acid (2) Diffuse WM abnormality
Tay-Sachs and Sandhoff (GM-2 gangliosidosis)	Lysosomal	Reduced beta-hexosaminidase enzyme→↑ GM2-ganglioside accumulation	Sandhoff (N-acetylhexosamine metabolite at 2.1) Thalamic T2 hypointensity Striatum T2 hyperintensity
X-linked adrenoleukodystrophy (ALD) *	Peroxisomal	Inability to oxidize long-chain fatty acids (VLCFA) into short-chain fatty acids →accumulation of long-chain fatty acids	Peri-trigonal T2 hyperintensity and restricted diffusion Posteroanterior & centrifugal gradient

CLINICAL CLUES

MRI

Zellweger syndrome *	Peroxisomal	Decreased dihydroxyacetone phosphate acyl transferase (DHAP-AT) activity. Peroxisomal function crucial to neuronal migration.	Lipids (0.87, 1.27) peri-sylvian polymicrogyria, germinolytic cysts
Biotin-thiamine responsive basal ganglia disease	Thiamine metabolism	Mutation in SCL19A3 gene encoding a thiamine transporter	Leigh-like phenotype Pyruvate (2.37)
Leigh disease (subacute necrotizing encephalopathy)	Mitochondrial	Multiple mutations in mitochondrial or nuclear DNA	↑ Lac (1.33) Pattern of symmetric basal ganglia or brainstem abnormalities
Leukoencephalopathy with brainstem and spinal cord involvement (LBSL)	Mitochondrial	Mitochondrial aspartyl-tRNA synthetase deficiency	↑ Lac (1.33), mI, Cho, ↓ NAA Diffuse cerebral volume loss, involvement of brain and spine
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) and POLG-related mitochondrial disorders	Mitochondrial	Mutations in mitochondrial DNA	↑ Lac (1.33) Non-territorial and basal ganglia "stroke-like" lesions Peri-rolandic parenchyma and thalami preferentially affected in POLG-related disorders
Pyruvate dehydrogenase complex (PDHc) deficiency *	Mitochondrial	Impaired pyruvate to acetyl-coA conversion and lactate accumulation	Pyruvate (2.37), ↑ Lac Leigh disease pattern Germinolytic cysts Periventricular necrosis
Molybdenum cofactor deficiency (MCD) and Sulfite Oxidase Deficiency (SOD)	Amino aciduria/Electron transport chain	Defect in amino acid metabolism, involved in electron transport chain	↑ taurine (3.2–3.4), ↑ S-sulocysteine (3.6), ↑ cysteine (2.9–3), ↑ Glx, ↑ Lac, ↑ Cho, ↓ NAA. Caudate head involved, thalamic sparing.

CLINICAL CLUES

MRI

Disorder	Classification	Defect + Metabolic Consequence	Key MRS Metabolite (ppm) or MRI Feature
Succinate dehydrogenase (SDH) deficiency *	Mitochondrial	Absent/insufficient oxidation of succinate →fumarate and electron delivery to the respiratory chain	Succinate (2.4), ↑ Lac (1.33) Leigh disease pattern
Alexander disease *	Leukodystrophy (Macrocephalic)	Astrocytopathy resulting in defect in myelin deposition	Frontal predominant WM disease and striatum involvement, enhancement, ↑ mI and sI
Canavan disease *	Leukodystrophy (Macrocephalic)	Inability to metabolize N-acetyl asparate (NAA) into asparate and acetate	↑↑ NAA Diffuse WM and thalamic lesions sparing striatum
Menke's Disease	Metal Metabolism	Copper metabolism Defect	Circle of Willis tortuosity and elongation universal, ± WM changes, vermian hypoplasia, atrophy, subdural collections
Pantothenate kinase associated neuro-degeneration (PANK)	Metal Metabolism	Neurodegeneration with brain iron accumulation	"Eye-of-the-tiger" sign—peripheral and central globus pallidus T2 hypointensity

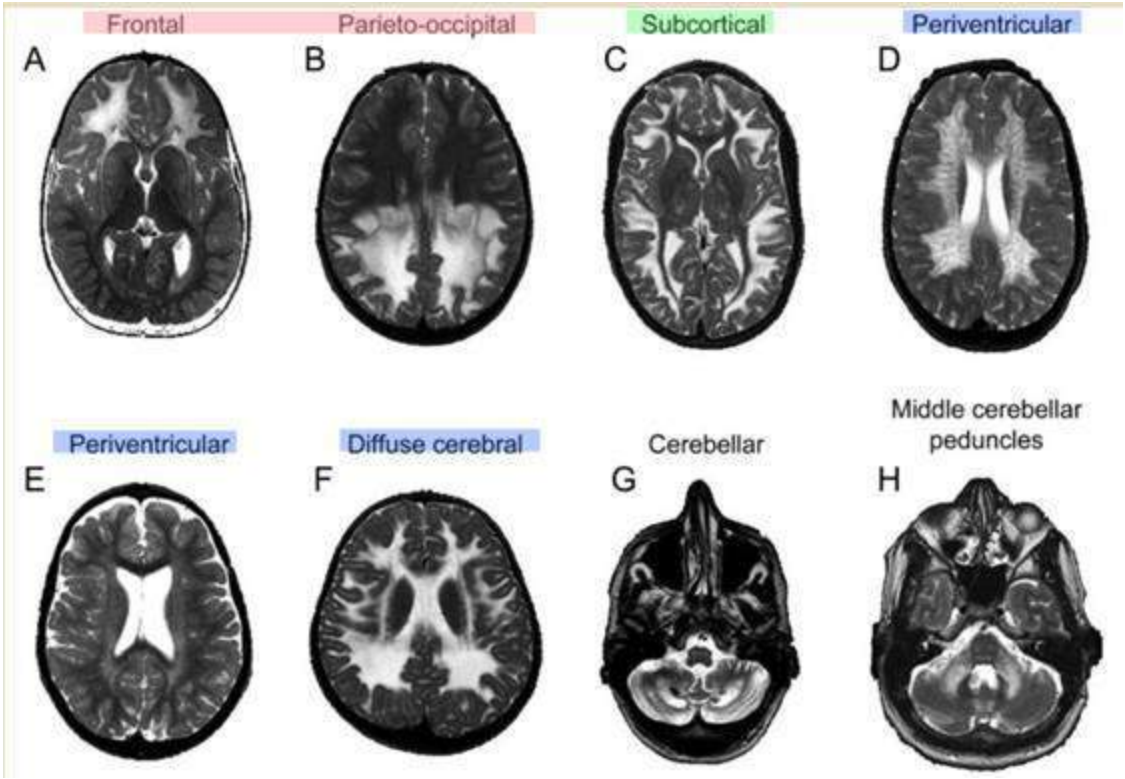
CLINICAL CLUES

MRI

Wilson's Disease	Metal Metabolism	Copper metabolism Defect	T1 hyperintensity in globus pallidus ± striatum and/or upper brainstem (11 years) T2 hyperintensity in putamen, globus pallidus, caudate, thalamus, brainstem (13 years)
Aicardi–Goutières syndrome	Miscellaneous	Defect in genes involved in nucleotide metabolism and/or sensing	Classic Triad: Calcifications, WM disease, atrophy Various other features correlate with genotype
Carnitine palmitoyltransferase (CPT)	Miscellaneous	Disorder of lipid metabolism	↑↑ Lipid
Creatine deficiency disorders *	Miscellaneous	Disorders of biosynthesis and transport of creatine	Reduced or absent Cr (3) MRI may be normal
Galactosemia *	Miscellaneous	Deficiency of galactose-1-phosphate enzyme →↑galactose-1-phosphate and galactitol	Galactitol (3.7): doublet at short TE, peak inversion at intermediate TE; ↓ mI
Congenital disorder of glycosylation Type 1a (CDG-1a)	Miscellaneous	Mutation in gene encoding PMM2 →abnormal glycosylation of N-linked oligosaccharides	Marked cerebellar volume loss with diffuse cerebellar T2 hyperintensity. Progressive volume loss of pons, cerebellum, and supratentorial WM. ↓ NAA/Cr ratio, ↑mI
Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies) *	Miscellaneous	Reduced glycosylation of Alpha-dystroglycan	Extensive malformations of cortical developmental (i.e., cobblestone lissencephaly, kinked z-shaped brainstem, midline pontine clefting)

CLINICAL CLUES

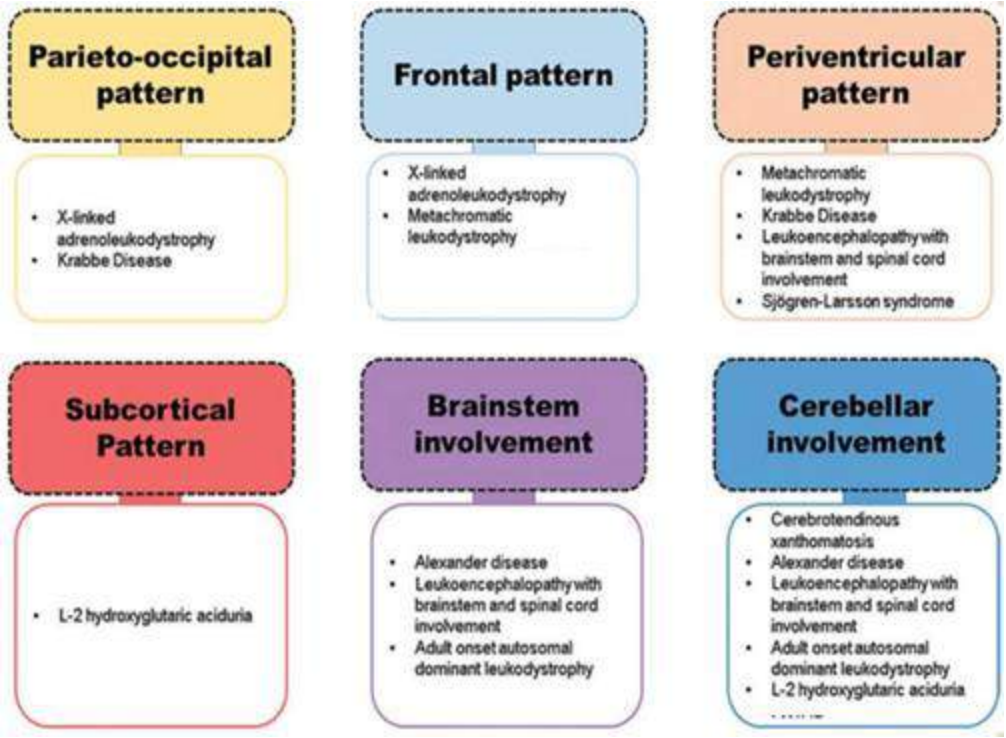
MRI



A: Alexander
B: XALD
C: Kearns sayre
D,E: MLD
F: NCL + canavan
G: CTX
H: ADLD

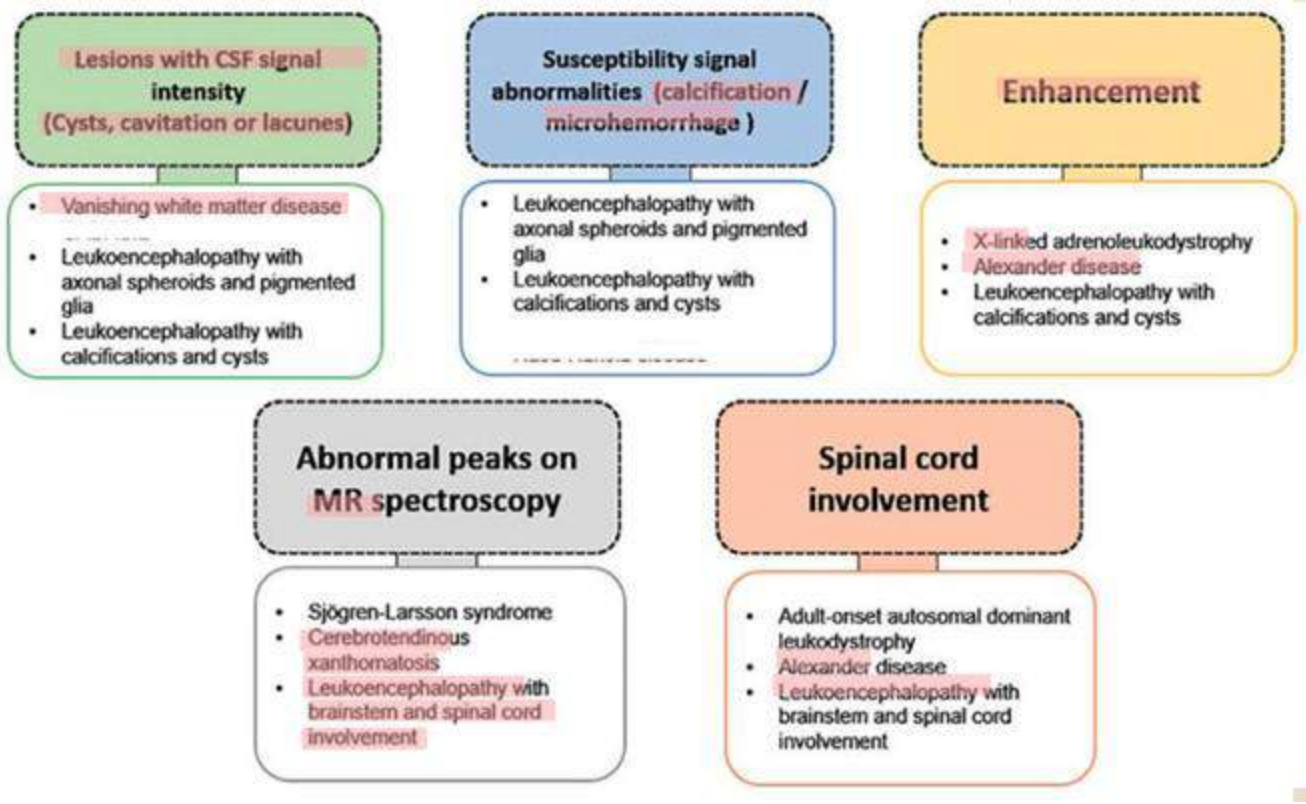
CLINICAL CLUES

MRI



CLINICAL CLUES

MRI

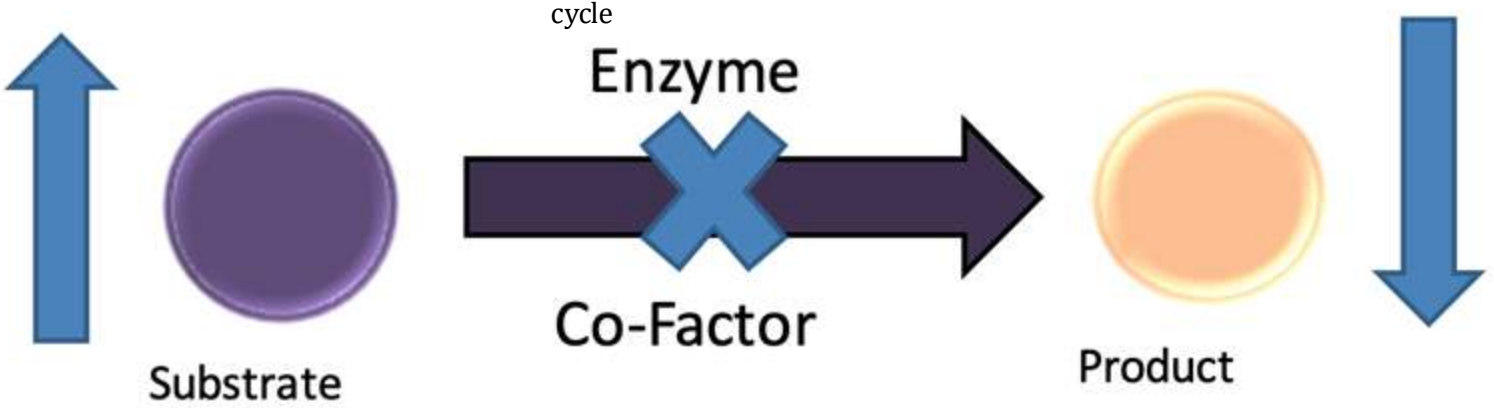


Treatment Concept in IEMs

Organic acidemia
Amino acidopathy
Galactosemia
Urea cycle disorders

Lysosomal Storage diseases
Organic acidemia
Amino acidopathy
Glycogen Storage disease Urea cycle

Glcyogen Storage disease Urea cycle defect
PKU



Substrata reduction

Dietary restriction
Alternative pathway
(Medication, dialysis)

Enzyme replacement or Cofactor replacement

IV Infusion ENZ
Liver transplant
Stem cell transplant

Replace deficient product

Oral/IV supplement

General Approach to IEM

(A) Given the frequent association of **certain triggering factors** with the development of acute decompensations, e.g. catabolic situations (infections, fasting, physical activity, childbirth, etc.), the intake of food that cannot be metabolized by the patient (proteins, fatty acids, etc.), or certain drugs, when facing an acute crisis in patients with an IEM > These factors should be quickly removed when possible.

(B) Laboratory evaluation:

- Blood tests: ammonia, blood gas, lactate, hemogram and biochemistry, and urine ketone.
- Genetic testing.

(C) Catabolism should be avoided: 10% dextrose at a rate of 3–4 mg/kg/min ASAP.

Notes:

- *Due to its ability to aggravate hyponatremia by dilution, 10% dextrose should be administered with caution (this is relevant in acute intermittent porphyria).*
- *Na inputs can be administered with (+) 0.9% NaCl added to 10% dextrose to avoid excess volume.*
- *If blood glucose >200 mg/dL, prioritize insulin rather than reducing glucose intake.*

General Approach to IEM

(D) Hyperammonemia and lactic acidosis should be urgently corrected.

1. **Metabolic acidosis** can be treated with bicarbonate.

2. **Hyperammonemia**:
   - Ammonia < 80 µmol/L > restriction of dietary protein intake should be sufficient.
   - Ammonia 80-200 µmol/L > use ammonium chelators
   - Impaired consciousness or hyperammonemia >200 µmol/L > hemofiltration.

(E) Treatment with specific cofactors and detoxifiers according to the particular disease in question should be carried out.

(F) Gene modifiers and therapies.

1. Dietary Restriction

AA	OA	UCD	FAO	Carbohydrate metabolism
PKU MSUD Homocystinuria	Propionic Acidemia Methylmaloonic Acidemia Isovaleric Acidemia Glutaric Aidemia	OTC, CPS NAGS, ASSD ASLD, AD	FAOD	Galactosemia Fructose intolerance Glycogen storage disease

2. Enzyme Replacement

Enzyme replacement therapy (ERT) has been FDA approved for use in several Lysosomal Storage Disorders (LSDs) including:

1.Gaucher Types 1 and 3
2.Mucopolysaccharidosis Type 1, 2 , 4, 6
3.NCL type II
4.Fabry Disease
5.Pompe Disease.

It involves replacement of the deficient enzyme by IV infusion of exogenous enzyme. It is recommended that it be used in LSDs without mental retardation because the exogenous enzyme does not cross the blood-brain barrier. ERT has proven to be effective in reducing many symptoms of LSDs.

3. Transplantation

Liver Transplant

- Urea cycle defect
- Organic acidemia (PA, MMA)
- MSUD
- Glycogen storage disease

Stem Cell Transplant

- Adrenoleukodystrophy
- Metachromatic leukodystrophy
- MPS Type-I
- Krabbe disease
- Gaucher disease (2+3)