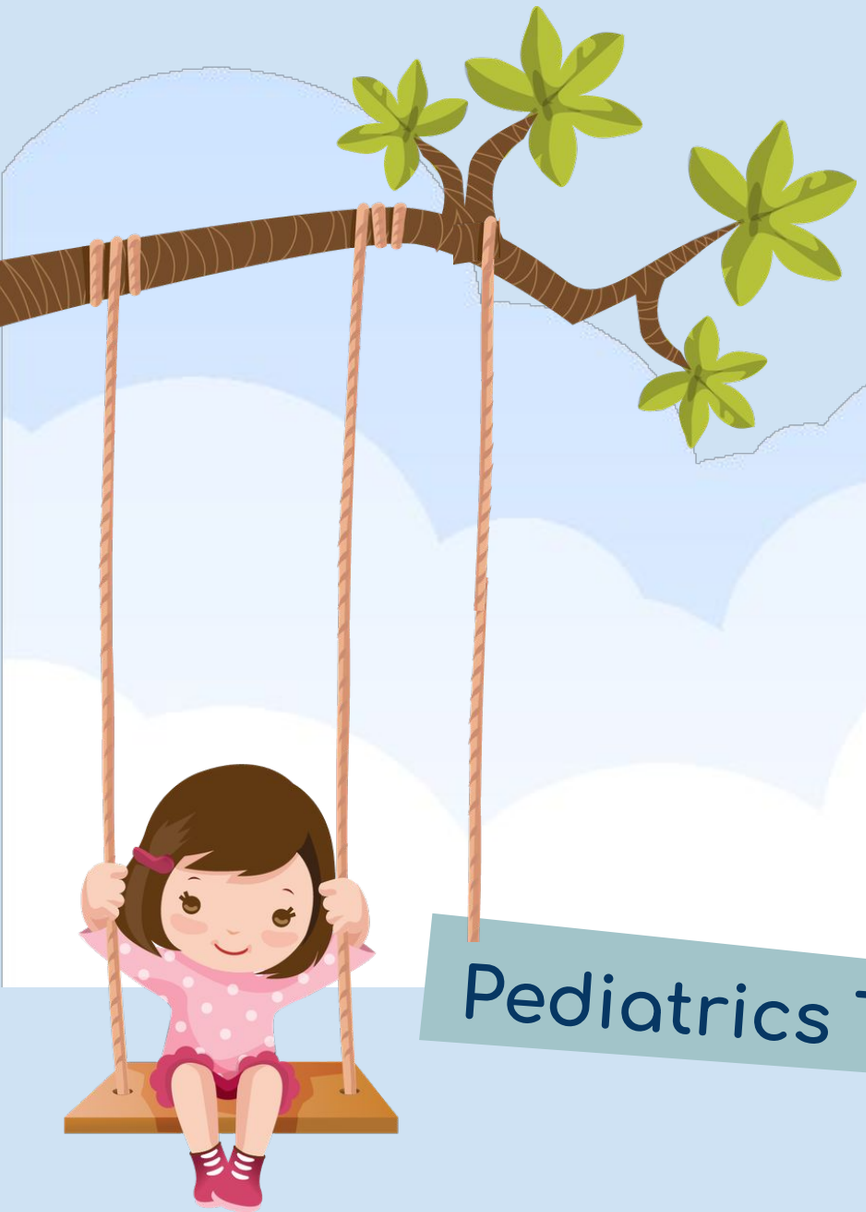

Pediatrics TeamWork

437

Metabolic Disorders

Done by:

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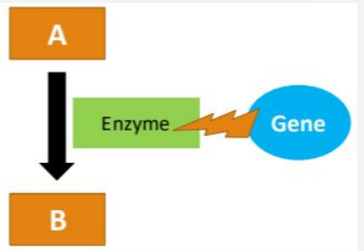
Aseel Badukhon

Notes Previous Notes Book Important!

Overview



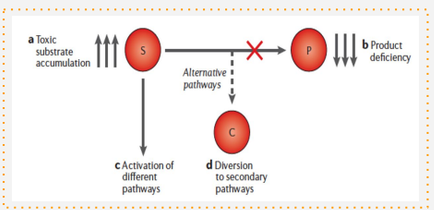
- Each of us is made of large complex molecules.
- They form tissues and organs.
- Molecules are NOT static
- Catalytic steps mediated by enzymes, encoded by genes
- Mutations in those genes, will lead to enzyme deficiency , leading to “inborn Error of Metabolism” Or metabolic disorders

Inborn Error of Metabolism (IEM)

- Group of congenital disorders caused by an inherited defect in a single specific enzyme that results in a disruption in a specific metabolic pathway.
- Individually rare, but collectively common. Eg. if there are 50 IEM each one of them are rare , لكن لما ناخذ الخمسين على بعض actually not rare

Mechanism of actions:

Direct toxicity of the accumulating substrate + Deficiency of the product + Activation of alternative pathways or diversion to secondary pathways leading to toxic byproducts



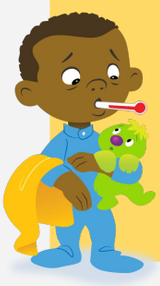
Clinical presentation (when to consider these dx in your ddx?)

- Consider in neonate with presumed sepsis or acidosis (usually high anion gap metabolic acidosis); older child with acidosis, lethargy
- Usually term infant, good APGAR score bc fetus using mother enzyme, once they born the problem start showing.
- Family Hx usually negative – may see consanguinity. -ve FHx doesn't rule out, +ve increase suspicion.We consider a couple of the same tribe as consanguinity.
- Sx – generally nonspecific with poor feeding, irritability, vomiting, seizures, progressing to lethargy, coma, apnea
- Occasionally specific sx/clues – urine odors, skin/hair

All autosomal recessive except OTC and Hunter disease those are X-linked disease

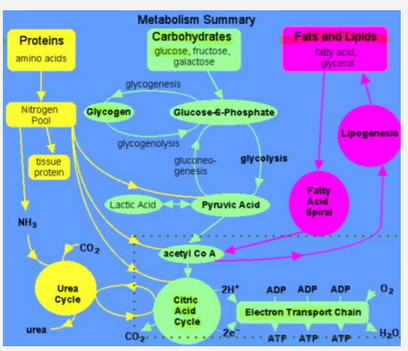
Differential Diagnosis of newborn with vomiting, lethargy, sz ...

- Amino acid disorders: MSUD
- Urea cycle disorders
- Organic acid disorders
- Carbohydrate disorders : congenital lactic acidosis, fructose disorders
- Mitochondrial disorders
- FAO disorders
- Other: (1 sepsis, adrenal insufficiency, 2 CHD, asphyxia, 3 metabolic)



-Think about sepsis, adrenal insufficiency, CHD and asphyxia first bc common is common then think about metabolic disorder (common in this order)

-**Sepsis more common than MD** especially in neonate



Complexity of inborn errors of metabolism

Disorders of Amino Acids

Types of amino acid

Essential & Non-Essential Amino Acids

Essential Amino Acids:
- Arginine
- Isoleucine
- Histidine
- Leucine
- Methionine
- Lysine
- Phenylalanine
- Tryptophan
- Threonine
- Valine

Non-Essential Amino Acids:
- Alanine
- Arginine
- Asparagine
- Aspartic Acid
- Cysteine
- Glutamic Acid
- Glutamine
- Glycine
- Proline
- Serine
- Tyrosine

What is the difference between essential amino acids and non essential?

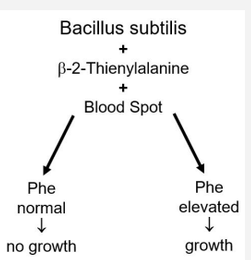
-Essential cannot be synthesized by our bodies, we get it from food
-Non essential that can be synthesized in our bodies

Amino acid metabolism disorders:

- Phenylketonuria
- Tyrosinemia type I
- Homocystinuria
- Glutaric aciduria type I

1.Phenylketonuria

- Robert Guthrie: 1916–1995
- Adapted the bacterial inhibition assay to newborn screening for PKU
- Leading advocate for NB screening we do this test to screen all newborns



Presentation

- Deficiency in phenylalanine hydroxylase
- Mousy odor
- Light hair/ skin bc tyrosine involved in Melanin production, so if the pathway blocked the **tyrosine will be deficient and phenylalanine will accumulate.**
- Seizures
- Developmental delay, Autism, intellectual disability
- White matter hyperintensities

Diagnosis: high phenylalanine, low tyrosine

PKU treatment

- "Diet for life"
- Restrict phenylalanine by restricting dietary protein Not 0 , not eliminate. Just reduce
- Supplement with phenylalanine-free medical food to guarantee the daily requirements
- Supplement tyrosine and other needed AA
- They have a good outcome and can live but when female get pregnant is bad due to teratogenicity

-Hypopigmentation of the skin and hair
-Ocular changes
-Nystagmus
-Reduced iris pigment
Foveal hypoplasia
-Tx: avoid sun, No dietary treatment

Albinism

Disorders of Amino Acids

1.Phenylketonuria

Maternal PKU

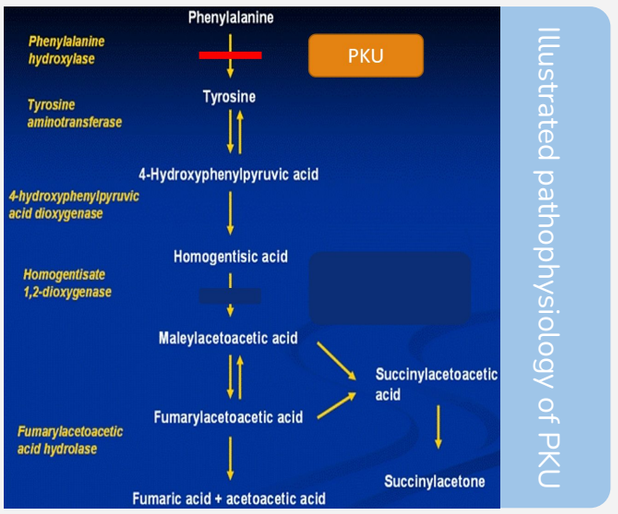
A teratogenic issue.

Symptoms:

- Microcephaly
- Cognitive disability
- Heart defects

Management:

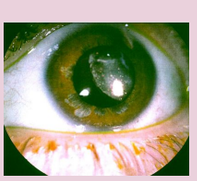
- Planned pregnancies
- Strict adherence to a low-phenylalanine diet
- Management begins prior to conception



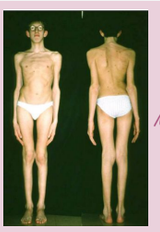
2.Others

Tyrosinemia type I	Homocystinuria	Glutaric aciduria type I
• Fumarylacetoacetate hydrolase deficiency for all disease here, , you don't have to remember enzymes name. • Can presents with liver or renal disease. **Treatment:** • NTBC • Phenylalanine and tyrosine restriction • Liver transplant if hepatocellular carcinoma develops	• Deficiency in the cystathionine B-synthase (CBS) • Marfanoid habitus (?v.s. Marian) you have to now the differences between them is an exam question. • patients will look like marfan tall, thin and long extremities compare with the trunk . • Eye abnormalities: Ectopia lentis- lens displaced downward while in marfan upward. Myopia • Developmental disability intellectual delay and developmental unlike marfan • Neuropsychiatric symptoms • Thromboembolism unlike marfan **Treatment** • Restrict dietary protein of Methionine and homocysteine	• Macrocephaly; fronto-temporal atrophy (from subdural hematoma ; you think **child abuse**. We do testing to make sure the patient doesn't have Glutaric aciduria type 1) • Acute encephalopathic crisis • IDD (intellectual and developmental disabilities), dystonia; MRI with basal ganglia changes and cortical atrophy • Defect in lys/Trp metabolism (glutaryl CoA dehydrogenase) • Dx urine organics with elevated glutaric, 3 OH glutaric • Rx low Lys/Try diet, carnitine

Always remember in metabolic disorder treatment is restoration not complete stoppage!!

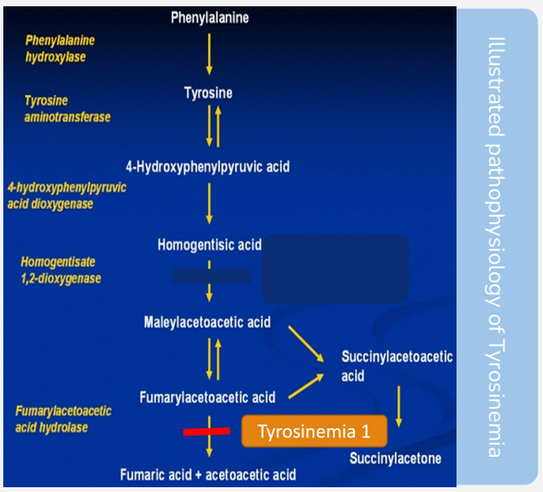


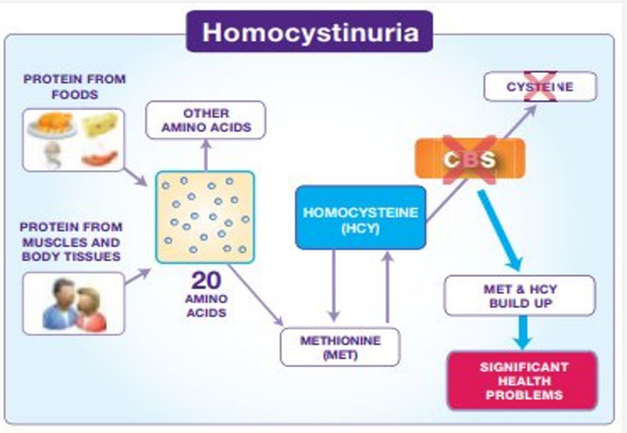
Ectopia lentis



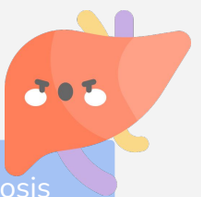
Marfanoid habitus

2.Others





Urea Cycle Disorders



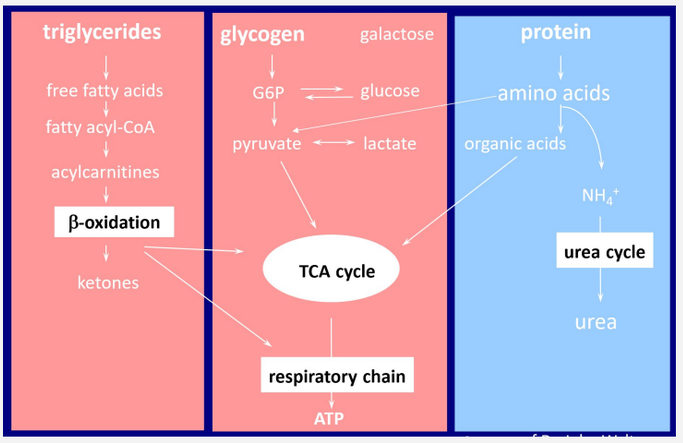
Urea cycle disorders are characterized by the triad of:

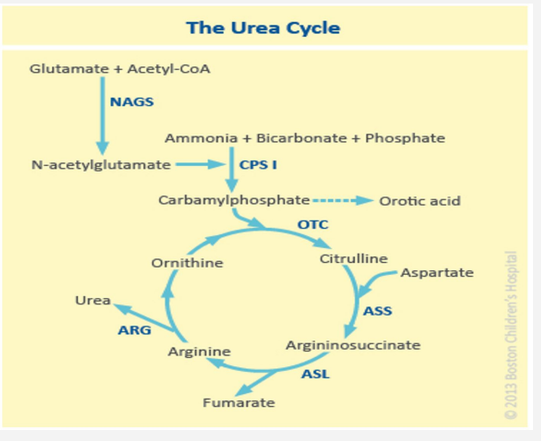
Hyperammonemia	Encephalopathy	Respiratory alkalosis

They all present with elevated ammonia

- It results from defects in the metabolism of waste nitrogen from the breakdown of protein and other nitrogen-containing molecules
- **It caused by deficiency of one of the following enzymes:**

Ornithine transcarbamylase (OTC)	Argininosuccinic acid synthetase (ASS)
Carbamyl phosphate synthase (CPS)	Argininosuccinic acid lyase (ASL)
N-acetylglutamate synthetase (NAGS)	Arginase





Everything before the block (before the deficiency) increases and everything after the block decreases.

Urea Cycle Disorders

Urea cycle defects presentations

- All can present in neonatal period, with NH3 except arginase deficiency
- AS lyase deficiency often develop hepatomegaly/fibrosis
- Arginase deficiency – spastic diplegia; IDD
- Lethargy
- Seizures
- Poor feeding
- Tachypnea
- High AMMONIA 1st DDX most specific
- Res Alkalosis ammonia will stimulate breathing -> they breathe faster ->wash out co2 , increase 02-> alkalosis

Urea cycle defects Labs

Remember this in the exam

	OTC dif	Citrullinemia	Argininosuccinic aciduria
Defect	OTC	ASS	ASL
Citrulline level	LOW	HIGH	HIGH
Argininosuccinic acid level	LOW	LOW	HIGH
Arginine level	LOW	LOW	LOW
Urine orotic acid	HIGH	NL	NL

OTC: Most common urea cycle defect, X-linked inheritance (male)

Treatment

- Restrict protein can be anything
- Arginine supp
- IV ammunol (Na benzoate and Na phenylbutyrate) in crisis ; respa alkalosis , metabolic acidosis , lethargic , dehydration , vomiting.
- Buphenyl (Na phenylbutyrate) – oral powder
- Ravicti (glycerol phenylbutyrate) – liquid
- Liver transplant not easy but main treatment , but still can have crisis and developmental delay.

Organic Acidemias

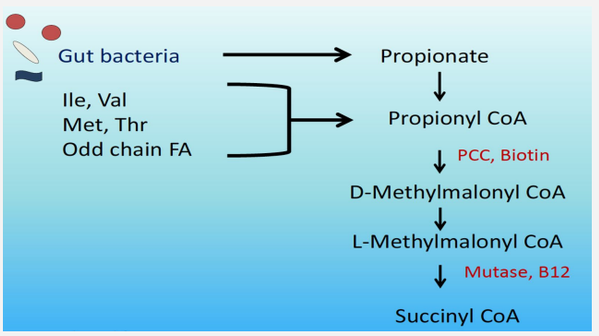
- It is due to deficiency of an enzyme in the branched chain amino acid catabolism.
- **Most commonly:**
  - Maple syrup urine disease- maple syrup smell
  - Isovaleric acidemia– Sweaty feet smell
  - Propionic acidemia
  - Methylmalonic acidemia
- Present in infancy with: lethargy, poor feeding, high ammonia, high anion gap metabolic acidosis. Ammonia not as high as urea cycle
- **Dx:** Urine organic acid
- **Treatment:** restrict protein, reserve catabolism, lower ammonia by ammonul

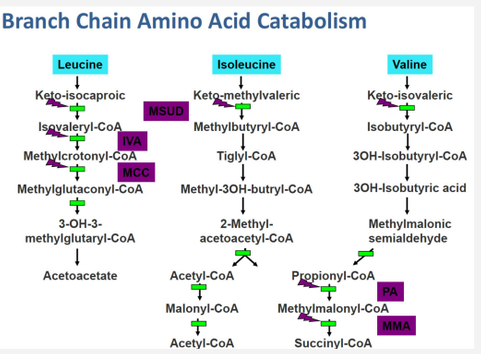
Organic acidemia vs Urea cycle

OA: high anion gap metabolic acidosis	Urea cycle: respiratory alkalosis

Propionic acidemia (PA) & Methylmalonic acidemia (MMA)

PA and MMA Metabolism





Complications	Treatment
• Bone marrow suppression during acute crises and as part of chronic disease • Severe feeding difficulties • Progressive renal disease • Cardiomyopathy • Basal ganglia infarcts “metabolic strokes” • Pancreatitis • Eye and vision problems	• low protein (Propimex) • restrict precursors [Val, Met, Ile, Thr, odd chain FA (VOMIT)] • carnitine • biotin • metronidazole • carbaglu • +/- B12

Organic Acidemias

Isovaleric Acidemia (IVA) & Maple Syrup urine disease (MSUD)

Isovaleric acidemia

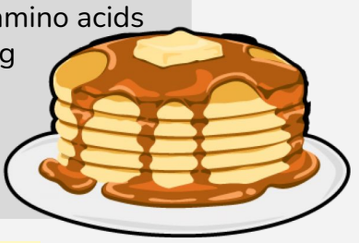
-Odor of sweaty feet

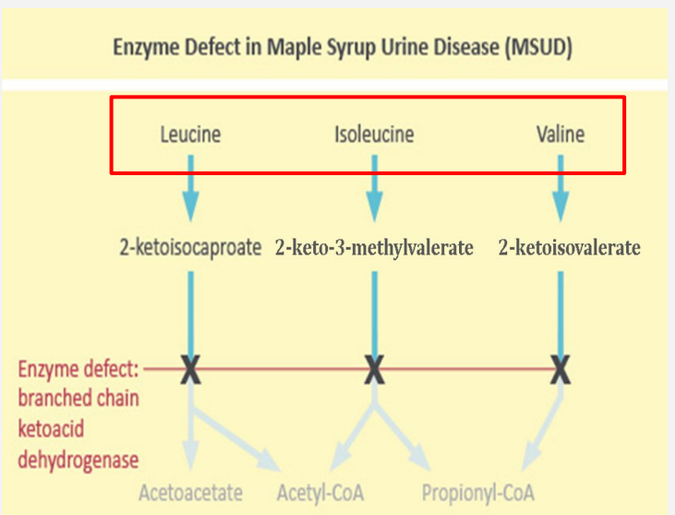
-UOA: isovaleric & 3 OH isovaleric acid; isovalerylglycine; ketones

-Rx low protein formula , glycine, carnitine

Maple Syrup Urine Disease

-Branched chain 2-ketoacid dehydrogenase deficiency
-Maple syrup smelling urine
-High valine, isoleucine, alloisoleucine, leucine
-Treatment: diet low of branched chain amino acids life long





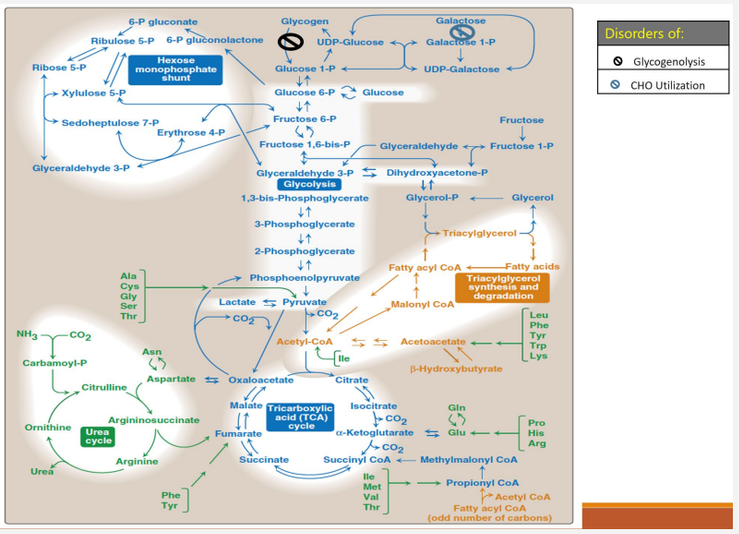
Dr. said know what is high and what is low;
(before the block and after)

Treatment of Metabolic Crisis

Vomiting , seizure , fever , lethargic

- ABC
- CAB
- Stop all source of protein central and parenteral nutrition. NPO
- Check GlucoChecks. ABG , Ammonia
- Insert an IV line and take blood for labs
- Ammonia blood sample should be taken with precaution because of high false positive rate (without tourniquet, in green-top tube, put on ice to the laboratory, separated within 20 minutes of collection and analyzed immediately).
- High caloric intake is the main stay of therapy: 1 1/2 to double maintenance I.V.F as D10 1/2NS + Kcl 30meq/l.
- Keep GlucoChecks 5-8mmol/L.
- Consider start **insulin** if hyperglycemia develop at dose of 0.01-0.05 unit/kg/hour and titrate up until blood glucose controlled. V similar to DKA
- Increase Carnitine dose to 300-400 mg/kg/day divided Q8 hours IV, orally or NGT.
- Do not decrease dextrose rate or amount and DO NOT STOP calorie delivery in the acute stage for any reason as this can precipitate hypoglycemia and catabolism which will further worsen the patient's condition.

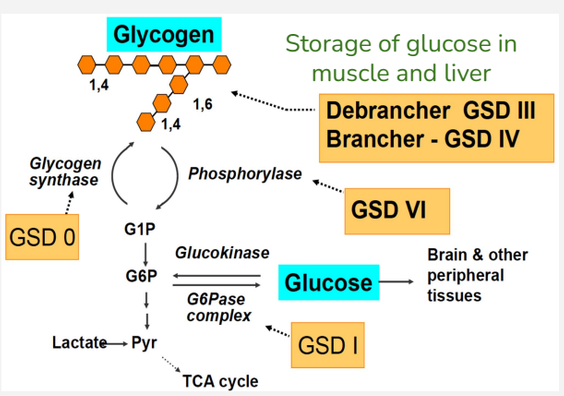
Disorders of Carbohydrate Metabolism

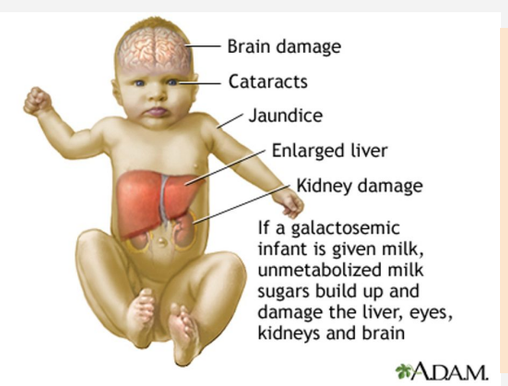


Galactosemia | GSD Ia (Von Gierke) | GSD II (Pompe disease)

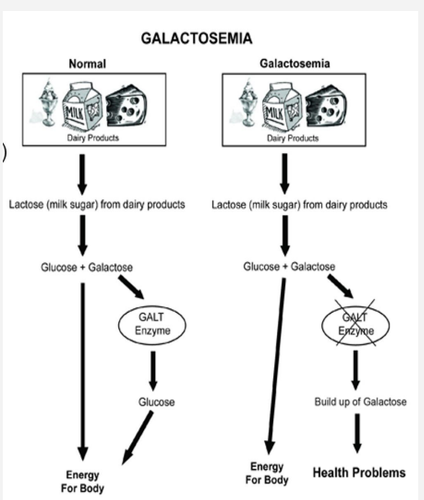
Galactosemia

- Deficiency of Galactose-1-phosphate uridyltransferase (GALT)
- **Treatment:** galactose and lactose free diet Formula. They can eat but need and can be measured.

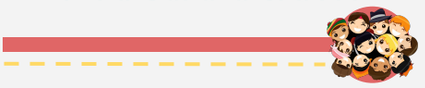




Clinical features



Disorders of Carbohydrate Metabolism

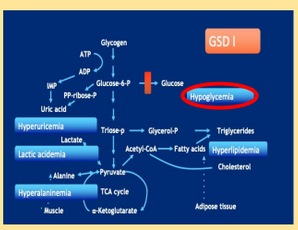


GSD Ia (Von-Gierke)

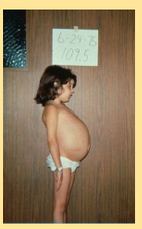
- Accumulation of glycogen and fat in the liver and kidneys they have **Hypoglycemia**. Glycogen is stored but not utilised.
- Deficiency of glucose-6-phosphatase (G6Pase) catalytic activity
- Developmental Delay, FTT
- Doll-like faces with fat cheeks, relatively thin extremities,
- short stature, protuberant abdomen, xanthoma and diarrhea
- bleeding tendency with frequent epistaxis.
- chronic neutropenia
- recurrent bacterial infections and oral and intestinal mucosal ulcers.
- Bone marrow suppression ; hepatomegaly . abdominal distention.

Management:

- freq. feeds of complex carbs do not fast because you can not use glycogen
- Sucrose (fructose and glucose) and lactose (galactose and glucose) are often limited or avoided
- Raw cornstarch, slowly absorbed glucose , between 6 months and 1 year
- Diet free galactose , we can't remove glycogen so we treat the symptoms.



Pyruvate (increased)
TGs (increased)
Hyperlipidemia



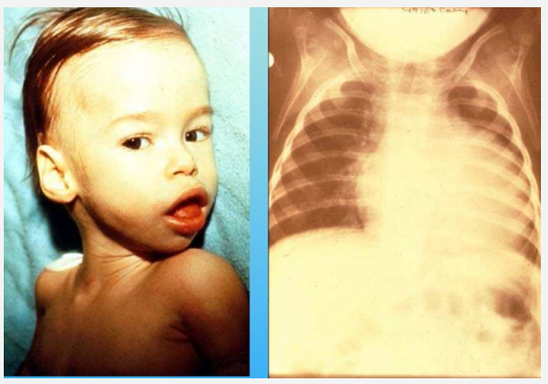
Ascites

الوجه مليان ،
اليد نحيفة

Pompe disease (GSD II)

- Disease of both glycogen storage (mechanism) and lysosomal storage (presentation)
- Lysosomal storage disease in the heart , glycogen storage
- Alpha glucosidase deficiency
- Glycogen deposits in liver, muscles and heart
- HSM hepatosplenomegaly
- Hypertrophic cardiomyopathy, cardiomegaly main cause morbidity and mortality
- Hypotonia
- FTT
- Macroglossia
- NO hypoglycemia because other glycogen stores can be broken down cause in the heart's glycogen

Treatment: Enzyme replacement therapy good outcome but expensive



Disorders of Carbohydrate Metabolism

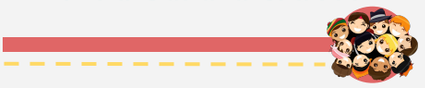


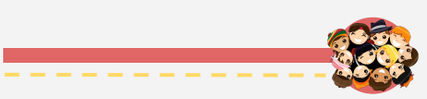
Table 21.1 Glycogen-storage diseases

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen	Branching enzyme (α-1,4 ⟶ α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.

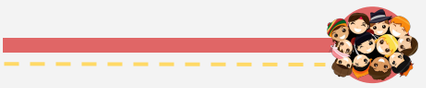
McArdle: Guy has pain when exercising, relieved by rest "second wave phenomena ".
They are at risk of exercise-induced breakdown of muscle tissue (rhabdomyolysis) and its complications, particularly acute kidney injury.

Lysosomal Storage Diseases



- Lysosomes cytoplasmic organelles that contain ~50 acidic degradative enzymes
- Deficiency results in accumulation of macromolecules usually degraded by that enzyme/protein.
- Stored material may cause enlargement of organs and may be visualized in membrane bound vesicles by EM
- Target organs affected by each disease are determined by normal sites of degradation of each compound
- Most patients are normal at birth; as material accumulates there is a plateau and then regression normal at birth (mom's enzyme) then decrease with time cause accumulation.

Lysosomal Storage Diseases



Types

- MPS hunter and hurler (mucopolysaccharidosis)
- Oligosaccharidoses
- Sphingolipidoses: GM1 gangliosidosis, GM2 gangliosidosis (Tay-Sachs/Sandhoff), NPC, Gaucher, Fabry
- Mucolipidosis
- Lipid Storage
- Neuronal ceroid lipofuscinoses
- GSD

Depends on the molecules that increases and decreases

Some General Phenotypic Features

- Coarse facies خشنة كأنه ملامح واحد كبير
- Organomegaly (liver, spleen)
- **Eye abnormalities:** Corneal clouding, Cherry red spot, Optic atrophy,
- Pigmentary retinopathy
- Skeletal abnormalities multiplex deposits
- Non immune hydrops

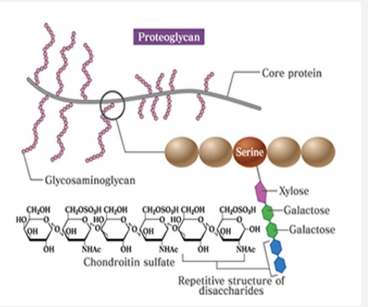
General Diagnostic Approach

- Serum lysosomal enzymes
- Blood smear
- Radiologic exam
- Ophthalmologic exam fundoscopic and slit lamp
- Urine mucopolysaccharides and glycoproteins
- Consider bone marrow in the past; abnormal cells
- Biochemical studies of fibroblast +/ leukocytes
- Molecular/gene sequencing best test

screening

1.Mucopolysaccharidoses (MPS)

- Defect lysosomal enzyme needing to break down glycosaminoglycans
- Progressive
- Coarse features, thick eyebrows, organomegaly, joint contractures, growth deceleration, deafness
- Dysostosis multiplex on x ray
- Hearing loss (sensorineural & conductive)
- Recurrent herniae, thickened mucous membrane
- Late cardiac involvement
- All autosomal recessive (MPS)except hunter x linked



Lysosomal Storage Diseases

1.Mucopolysaccharidoses (MPS)

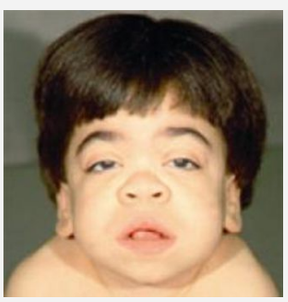
MPS features

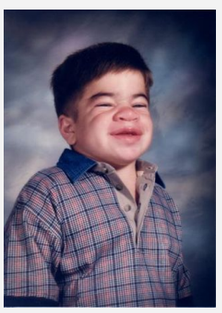
- **Hurler (MPS I)**- Growth deceleration, corneal clouding, HSM, pes cavus, hirsutism
- HUNTER (MPS II)- skeletal anomalies, NO corneal clouding
- SANFILIPPO (MPS III)- behavioral problems
- MORQUIO (MPS IV)- normal IQ, skeletal involvement

Treatment: HSCT, Enzyme replacement therapy for treatment unlike sanfilippo and hunter

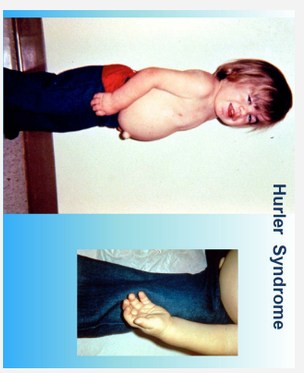
Other Features of MPS Disorders

- Hydrocephalus
- Obstructive airway disease; difficulty with intubation; excessive secretions
- Atlantoaxial instability; odontoid hypoplasia
- Cardiac disease valvular, conduction disturbances, cardiomyopathy
- Pulmonary and systemic hypertension





Coarse features happen with time



2. GM2 Gangliosidosis

- Tay Sachs,jews Sandhoff arab
- Def. hexosaminidase A/B enzyme
- Progressive neurological deficits
- Normal till 9 months then show developmental regression
- Hypotonia , Macrocephaly
- Exaggerated startle response أي فزة يبالغ فيها الطفل مو طبيعي
- Cherry red spots
- No organomegaly
- Die early
- Ashkenazi jews أمراض اليهود
- No treatment

Cherry red spot

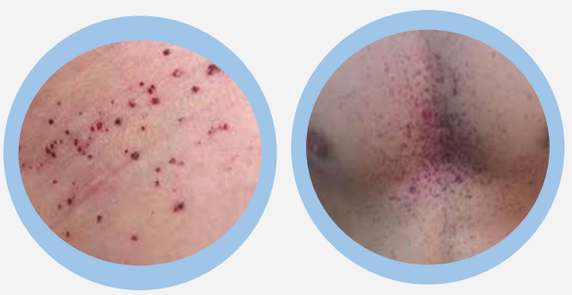
Lysosomal Storage Diseases

3.Niemann Pick

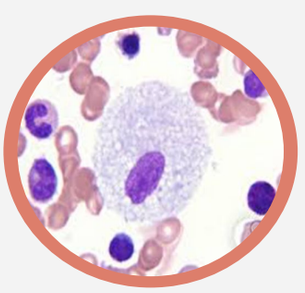
Niemann-Pick A, B	Niemann-Pick C
• Sphingomyelinase def. • CNS problems – hypotonia • HSM* (vs. Tay Sachs) no HSM in tay sachs • Cherry red spots both they have • Interstitial lung disease • Death by 4 years • Dx- foam cells (Niemann Pick cells) in bone marrow not diagnostic • No treatment *Hepatosplenomegaly	• Disorder of cholesterol trafficking cholesterol storage • **Juvenile:** ataxia, speech delay, HSM, progressive intellectual decline, dystonia • **Adult onset**- ataxia, dystonia, psychiatric, hepatomegaly • It is mainly neurological manifestations • Dx- foam cells (Niemann Pick cells) in bone marrow • Tx- miglustat helps not curative

4.Fabry disease and Gaucher's disease

Fabry disease Doctor skipped	Gaucher's disease
• X-linked • Males– median age of onset 9 yrs; peripheral neuropathy; acroparesthesias; angiokeratomas; lens/corneal opacities • **late manifestations:** renal and cardiovascular disease; chronic lung disease with fibrosis • Accounts for ~1% chronic renal failure & 5% cryptogenic stroke; incidence cardiac variant • Most females have sx – median age of onset 13 yrs; fatigue, stroke, ~10% females develop renal failure • **Tx**- ERT (agalsidase beta)	• Dif. Beta-glucocerebrosidase enzyme • 3 types based on clinical symptoms: - **Type I non neuronopathic**; splenomegaly, pancytopenia, bone pain/lytic bone lesions - **Type II acute neuronopathic:** rapidly progressive neurologic disease with hepatosplenomegaly - **Type III subacute neuronopathic** later onset • Dx "foam macrophages" in bone marrow, smear; enzyme assay • **Treatment**- Rx symptomatic; splenectomy; ERT for Type I pts (no effect Type II)



Angiokeratoma



Foam cells

Bone marrow problem
- Pancytopenia
- Bone pain

Lysosomal Storage Diseases

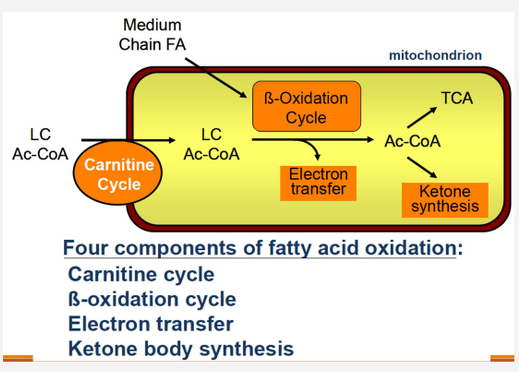
Differential diagnoses!

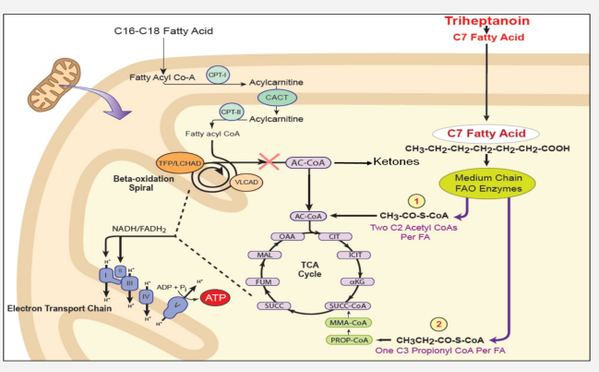
Cherry red spot 🍒	Foam cells in bone marrow 🍳
• Tay Sachs Disease • Sandhoff Disease • Sialidase deficiency (mucolipidosis type 1) • Niemann Pick Disease Type A • GM1 Gangliosidosis **A mnemonic to remember other causes of cherry red spot: (EXTRA)** Cherry Tree Never Grow Tall Central retinal artery occlusion, Tay sachs disease, Niemann Pick disease, Gaucher's disease, Trauma (Berlin's edema)	• Niemann–Pick disease (types A, B, C, D) • Gm1 gangliosidosis (type 1) • Gm2 gangliosidosis (Sandhoff variant) • Mucolipidosis • Fucosidosis • Mannosidosis • Neuronal ceroid-lipofuscinosis • Chronic hyperlipidemia • Chronic corticosteroid therapy • Hematologic malignancies (e.g., Hodgkin disease, leukemia, myeloma) • Hematologic disease (e.g., aplastic anemia, ITP)

Most of lysosomal diseases show foam cell thats why is not good way to diagnose. We do genetic confirmatory to diagnose

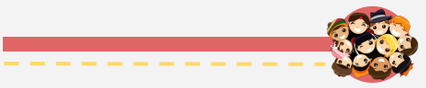
Fatty Acid Oxidation

- During fasting FAO provides up to 80% total body energy needs
- Long chain (LC) fats preferred substrate for cardiac and skeletal muscle
- LC free fatty acids (FA; C18, C16) released from TG in adipose tissue
- Peripheral tissues oxidize FA to CO2 and H2O Liver oxidizes FA to ketone bodies for energy for gluconeogenesis and ureagenesis
- Ketone bodies used as fuel in CNS





Fatty Acid Oxidation



- Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
- Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD)
- Very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
- Baby presents with Non-ketotic hypoglycemia, high ammonia (not as high as urea cycle), high CK, liver involvement, cardiomegaly(cause they all need high energy),Normally high ketone

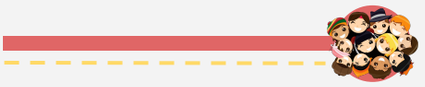
Treatment: low fat formula because they can't utilize it
brain uses glucose , not available? ketones

- coagulopathy
- enlarged liver, fasting intolerance
- Cardiac cardiomyopathy, arrhythmias
- Sudden death liver (hypoglycemia),
- Acute rhabdomyolysis muscle need energy they take fat
- Chronic – weakness, fatigue, lactic acidosis
- Risk HELLP (hemolytic anemia with elevated LFTs and ow platelets) in females with LCHAD fetus
- Elevated CK-MB

Summary (:

Disorder	Glucose	NH3	Ketones	Acidosis	Note
Organic acidemia	LOW	HIGH (usually)	++	High AG met acidosis	- Early DOL2 -thrombocytopenia, pancytopenia, neutropenia -dehydration (PA, MMA) -IVA (sweaty feet)
Urea cycle	NL	HIGHHH	NO	NO	-Hypotonia -tacypnea
FAO	LOW	NL/HIGH (prot. Breakdown)	NO	NO	- + stress, illness, fasting - Nonketotic hypoglycemia - Hepatomegaly
GSD I (von Gierk)	LOW	NL	++	High AG met acidosis	- Pt cant breakdown glycogen. They dep on fats, prot, anarobic metabolism - HSM, doll-faces - High uric acid
Amino acidopathy	Nl	Nl	NO	NO	- PKU (mousy odor, light color skin), alkaptonuria (black urine), Homocystinuria (marfanoid, clots)
Galactosemia	LOW	NL	NO	NO	- 1st wk, vomiting, diarrhea, sz, jaundice, HSM, **cataract**, DD -Galactose deposit in kidney, liver, brain -Increase risk f gram negative sepsis (E.coli)

Questions



A two-week-old female infant presents with a several day history of lethargy and poor feeding, with repeated vomiting. The infant was a product of a normal pregnancy and an uneventful vaginal delivery. Birth weight was 3810 gm; today's weight is 3520 gm. The infant is jaundiced, and has a weak, high-pitched cry. The liver edge is palpable 2 cm below the right costal margin.
Complete blood count is unremarkable. Total indirect (unconjugated) bilirubin is elevated. Urine is positive for reducing substances when tested by the clinitest method, although a standard urinalysis is unremarkable. Blood glucose is 42 mg/dl. **Which of the following is the most likely diagnosis?**

- Sepsis
- Subdural hematoma
- Formula intolerance
- Neonatal hepatitis
- Galactosemia

a 7-day-old male infant; he was born at term. He is the 3.5 kg product of an uncomplicated pregnancy, labor and unassisted vaginal delivery of a 27-year-old g2p1ab0 woman; the patient presents with the sudden onset of vomiting, lethargy, and tachypnea. He is bottle-fed and was feeding vigorously until today. He has had no fever, rhinorrhea, cough, diarrhea, or abdominal distention. An older sister had the onset of similar symptoms at 5 ½ years of age, as did their mother, in both of whom these symptoms would recur episodically, usually with an intercurrent infection. A maternal uncle died in infancy with very similar symptoms; he also experienced seizures. Examination reveals a normal temperature, a pulse of 134, a blood pressure of 88/52 mm hg, and a respiratory rate of 62. He is lethargic. The anterior fontanelle is slightly sunken. There is mild skin tenting and moderate hypertonia. The lungs are clear. There is no organomegaly or petechiae. You obtain blood, urine, and cerebrospinal fluid cultures, all of which are pending. Cerebrospinal fluid cell count, glucose, and protein are normal. Chest radiography is normal. An arterial ammonia level is 1,650 mcg/dl. Ketones are normal.

What type of disorder best accounts for this patient's clinical picture?

- UCD ammonia elevated , family hx, OTC most common x linked(males severe, female mild)
- Aminoacidopathy
- OA
- FAO ketones normal
- Lysosomal storage

You are asked to evaluate a 4-day-old male infant; he was born at term. He is the 3.1 kg product of an uncomplicated pregnancy, labor, and unassisted vaginal delivery of a 24-year-old g1p0ab0 woman. There was a positive newborn screening test for phenylketonuria (PKU). The child's mother reports that he appears to be completely well; he has been breast feeding without difficulty or vomiting. Physical examination is entirely normal.

What would you tell this child's mother?

- Most positive results are FP, need to repeat screen in 2 weeks
- Since child is feeding well, no need for further evaluation
- He child need to start immediately on phe- restricted diet
- Most positive results are true positive, so most likely your son has PKU
- He child needs plasma phe and tyrosine level she has + screening test so we do confirmatory (we can not act upon it and give meds unless + symptoms)

Book!

Table 27.3 Typical first line investigations (guided by clinical picture)

Sample	Test	Indication
Blood	Amino acids and acylcarnitines	Suspected urea cycle disorders, organic acidaemia or aminoacidopathy – presenting with developmental delay, seizures, faltering growth, dysmorphism
	Ammonia	Suspected urea cycle disorder
	Beutler screening test or Gal-1-PUT Assay	Suspected galactosaemia
	Very long chain fatty acids	Suspected peroxisomal disorder
	White cell enzymes	Dysmorphism, organomegaly, learning difficulties, developmental regression
	Lactate	Suspected mitochondrial disease, glycogen storage disorders
Urine	Organic acids	Organic acidaemia, fatty acid oxidation disorders
	Amino acids	Tubulopathy, cystinosis
	Glycosaminoglycans and oligosaccharides	Mucopolysaccharidoses or oligosaccharidoses

- Metabolic acidosis can be a presenting feature of inborn errors of metabolism (IEM), and a metabolic acidosis is more likely due to IEM if:
  - There is severe acidosis disproportionate to the usual clinical condition
  - Abnormalities persist despite standard management
  - There is a raised anion gap
- Infection is a common trigger for the presentation of an IEM. Both may require concurrent investigation and treatment
- Always consider an IEM if:

Unexplained encephalopathy and/or markedly raised anion gap

Sudden unexplained death of infancy

- **An ammonia level should be measured when there is:**
  - unexplained encephalopathy
  - respiratory alkalosis because it is a respiratory stimulant
  - recurrent vomiting
  - unexplained severe illness in a baby or child
  - unexplained seizures as it causes cerebral oedema

- Ammonia can be elevated in severe illness, liver disease, by certain medications, and transiently in the newborn
- Principles of management of hyperammonemia are to stop feeds, start 10% dextrose, give intravenous ammonia scavenging medications and arginine to support the urea cycle, and arrange urgent transfer to paediatric intensive care for haemofiltration.
- Lactate is raised because it acts as an alternative fuel
- **Mucopolysaccharidoses:** Once the diagnosis is suspected the initial test is measuring the excretion in the urine of the major storage substances, the glycosaminoglycans (GAGs). This is followed by lysosomal enzyme testing and genetic testing. Successful enzyme replacement by hematopoietic stem cell transplantation has been performed for MPS type I, **but it cannot reverse any established neurological abnormality and has a minimal effect on the skeletal component**.

Book!

Mucopolysacharidoses

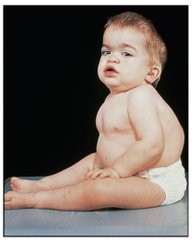


Figure 27.1 Untreated Hurler syndrome showing the characteristic facies and skeletal dysplasia. The prominence of the lower spine is called a 'gibbus'.

Table 27.7 Clinical features of mucopolysaccharidoses

Eyes	Corneal clouding
Skin	Thickened skin
	Coarse facies
Heart	Valvular lesions
	Cardiomyopathy
Neurology	Developmental regression
Skeletal	Thickened skull
	Broad ribs
	Claw hand
	Thoracic kyphosis
	Lumbar lordosis
Other	Hepatosplenomegaly
	Carpal tunnel syndrome
	Conductive deafness
	Umbilical and inguinal hernias

Table 27.8 Types of mucopolysaccharidoses

Type	Inheritance	Cornea	Heart	Brain	Skeletal
MPS I (Hurler)	AR	+++	++	+++	++
MPS II (Hunter)	X-linked	–	+	++	+
MPS III (Sanfilippo)	AR	±	–	+	+
MPS IV (Morquio)	AR	+	+	–	+++
MPS VI (Maroteaux–Lamy)	AR	+++	++	–	++

AR, autosomal recessive.

Table 27.9 Some mitochondrial disorders

Syndrome	Clinical features	Onset
MERRF	Myoclonic epilepsy with ragged red fibres.	5–15 years
MELAS	Mitochondrial encephalopathy, lactic acidosis, stroke-like episodes. Myopathy, migraine, vomiting, seizures, visual and hearing disturbance.	5–15 years
Alpers	Intractable seizures and liver involvement.	Early childhood

- **Mitochondrial disorders** are those directly resulting from deficits in energy production by oxidative phosphorylation and therefore affect those organs with the greatest energy demands, i.e. brain, heart, kidney, retina, skeletal muscle
- Investigations of mitochondrial disorders: it is difficult and often only symptomatic treatment is possible.
- Consider mitochondrial disease when there is:

Multisystem disease

Elevated lactate, though differential diagnosis is wide, and it is not always present

MRI brain scans showing characteristic features

- The most common reason for raised cholesterol in childhood is obesity
- Familial hypercholesterolemia is the most common inherited disorder of lipid metabolism; it can be either homozygous or heterozygous
- **Homozygous familial hypercholesterolemia** typically presents before the age of 5 years of age to dermatologists with lipid deposits. These deposits classically occur in the natal cleft and the extensor surfaces of the elbows. The risk of MI and stroke in the early teenage years is extremely high. **Treatment:** low fat diet, statin and ezetimibe. If no response, go for lipid apheresis or liver transplantation.
- **Heterozygous cases** usually detected because either of parents had an MI. **Treatment** of heterozygotes is with the use of a low fat diet and, from the age of 8 years, a statin.
- Abnormally low lipid levels can also be an indicator of metabolic disease, e.g. abetalipoproteinemia.

Table 27.10 Summary of the features of lipid storage disorders

Disorder	Enzyme defect	Clinical features
Fabry disease	Alpha-galactosidase A	Only X-linked lipid storage disorder
		Males: present in childhood with recurrent acute pain/paraesthesiae in limbs, diminished sweating, angiokeratomas, normal intelligence
		Females: 70% asymptomatic. Presentation tends to be from age 15 years onwards
		Enzyme replacement therapy
Gaucher disease	Beta-glucosidase	Occurs in 1 in 500 Ashkenazi Jews
		Chronic childhood form – splenomegaly, bone marrow suppression, bone involvement, normal IQ
		Splenectomy may alleviate hypersplenism
		Enzyme replacement therapy
		Acute infantile form – splenomegaly, neurological degeneration with seizures
		Carrier detection and prenatal diagnosis are possible
Niemann–Pick disease type C	Cholesterol trafficking disorder	Infantile: neonatal liver disease with hepatosplenomegaly. Usually improves but may be fatal
		Juvenile: age 3–15 years with progressive ataxia, language delay, hepatosplenomegaly, vertical supranuclear gaze palsy, cherry red spot (50%). Death 7 years to adulthood
		Adult: ataxia, dementia, psychiatric illness
		Treatment with substrate reduction therapy
Wolman disease	Lysosomal acid lipase	Neonatal presentation with severe growth faltering, steatorrhoea, massive hepatosplenomegaly and X-ray shows adrenal calcification
		Fatal within first year
		Newly developed enzyme replacement therapy