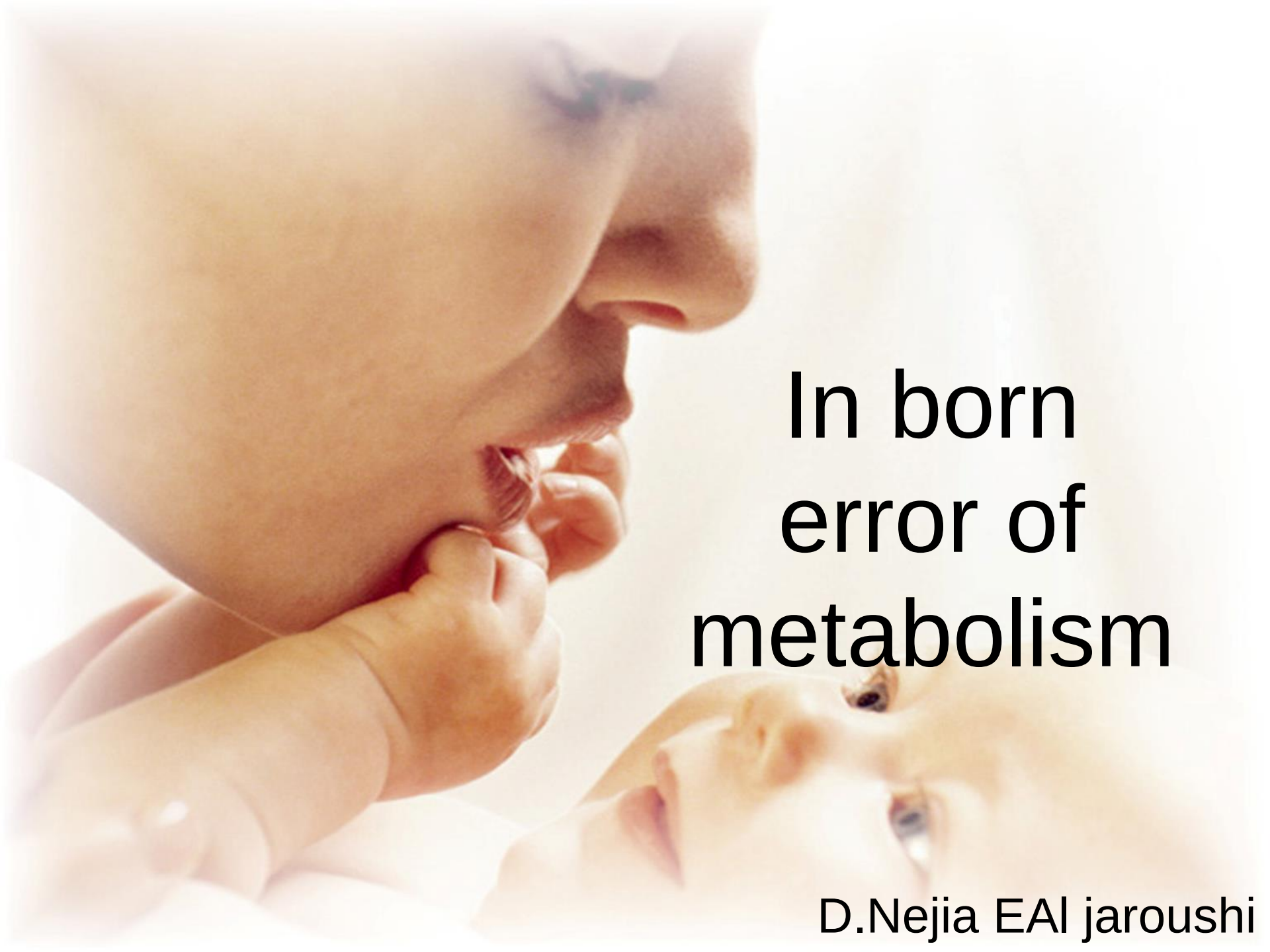


In born error of metabolism

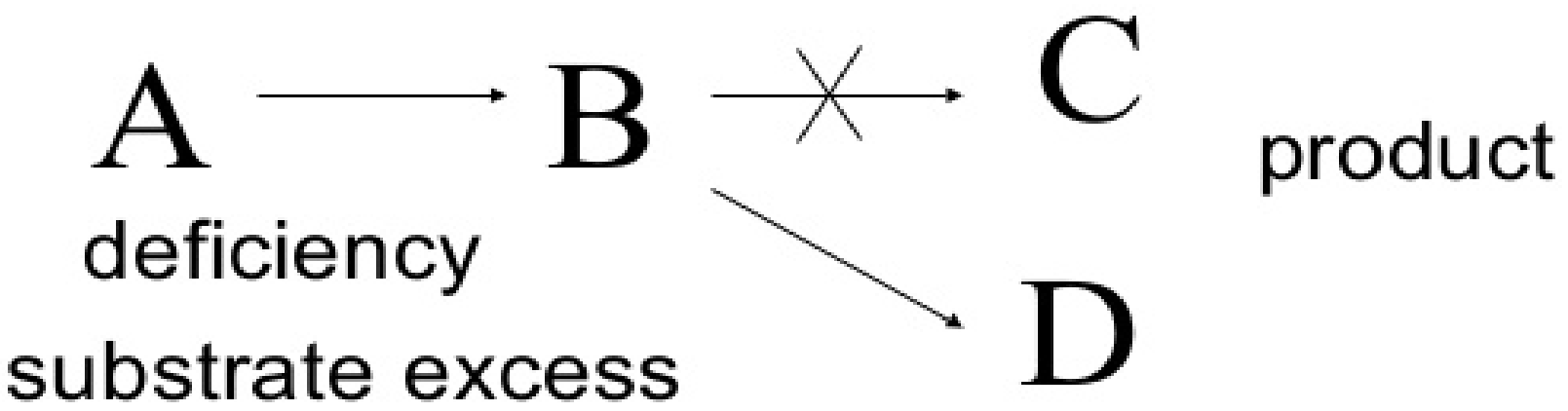
D.Nejia EAl jaroushi

In born error of metabolism

- IEM---an inherited enzyme deficiency leading to disruption of body metabolism
- The majority are due to defects of single gene that code for enzymes that facilitate conversion of various substance (substrate) in to others (product)
- In most of the disorders, problems arise due to accumulation of substance which are toxic or interfere with normal function or reduce ability to synthesize essential compound.

What is a metabolic disease?

- Garrod's hypothesis



IEM ,means disorders in which there’s block at some point in the normal metabolic pathway

Problem either in---enzyme

---receptor

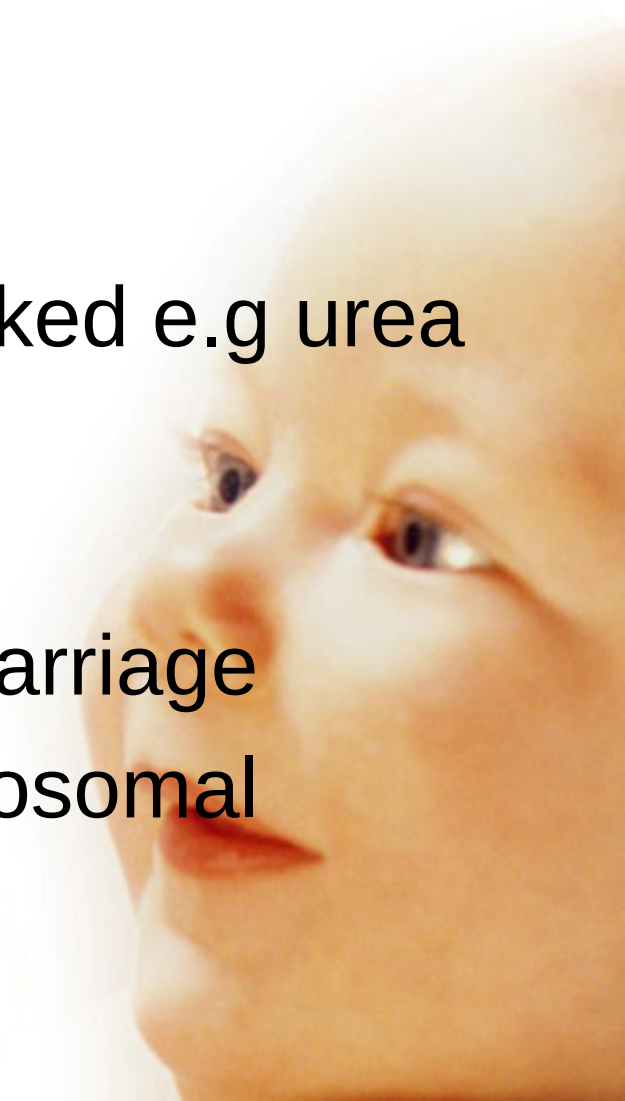
---transport vehicles

---membrane pump

---structure element

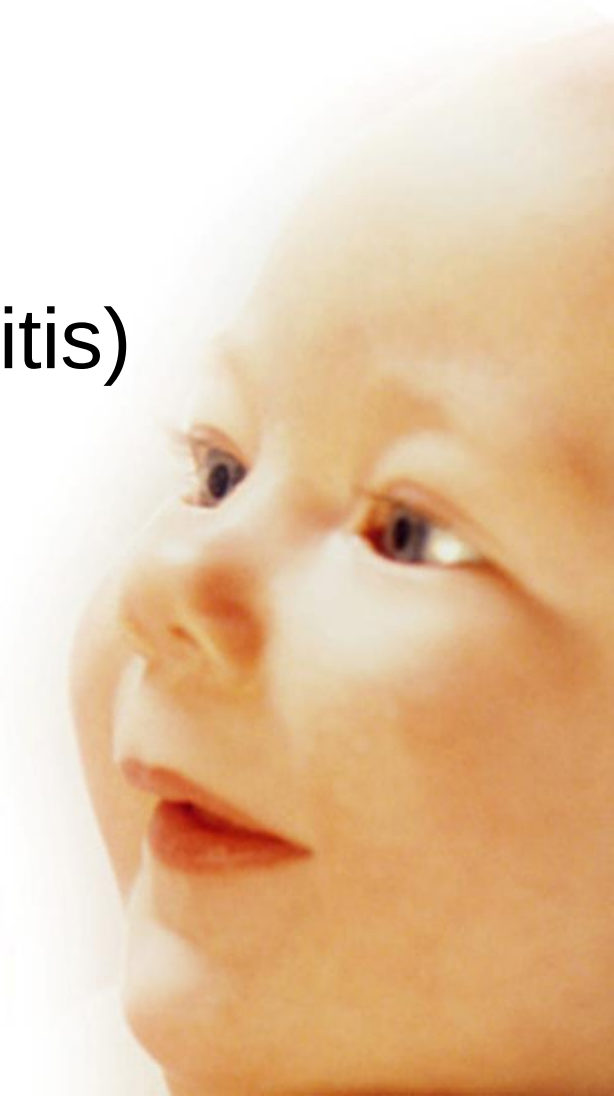
Clinical clues

- From history
- Neonatal deaths ,fetal losses
- Maternal family history (X-linked e.g urea cycle)
- +ve family history can help
- History of consanguineous marriage
- (most of IEM inherited as autosomal recessive



- Progressive symptoms.
- Perinatal history, early newborn period normal, usual baby full term .
- Symptom started after introduction and progression of feed
- Sick baby not respond to treatment

- D/D of IEM
- 1-bacterial sepsis
- 2- acute viral infection
- 3-birth asphyxia
- 4- CNS (hemorrhage, meningitis)
- 5-viral hepatitis
- 6-cardiomyopathy
- 7-neuromuscular disorder



Clinical presentation

- Baby comes with history of
- poor feeding,
- vomiting, lethargic , irritability
- convulsion ,coma
- respiratory distress,
- jaundice , coarse feature
- unusual odor
- sudden infant death
- Hepatomegaly or hepatosplenomegaly
- cardiomyopathy,

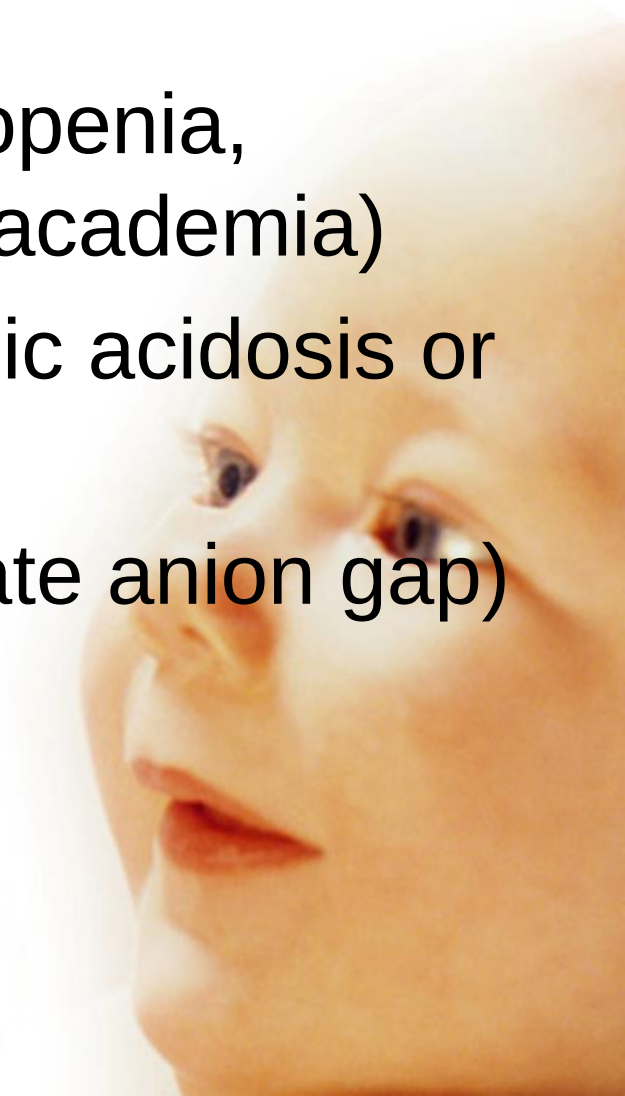
- Older children come with ;;
- failure to thrive ,
- mental retardation ,
- regression of growth
- encephalopathy .

Inborn Errors of Amino Acid Metabolism Associated with Peculiar Odour:

INBORN ERROR OF METABOLISM	URINE ODOR
Glutaric acidemia (type II)	Sweaty feet, acrid
Hawkinsinuria	Swimming pool
Isovaleric acidemia	Sweaty feet, acrid
Maple syrup urine disease	Maple syrup
Hypermethioninemia	Boiled cabbage
Multiple carboxylase deficiency	Tomcat urine
Oasthouse urine disease	Hops-like
Phenylketonuria	Mousey or musty
Trimethylaminuria	Rotting fish

Investigation

- Blood for
- Complete blood count (neutropenia, thrombocytopenia in organic academia)
- Arterial blood gases (metabolic acidosis or respiratory alkalosis)
- Serum electrolytes (to calculate anion gap)
- Ammonia
- Lactate and pyruvate ratio

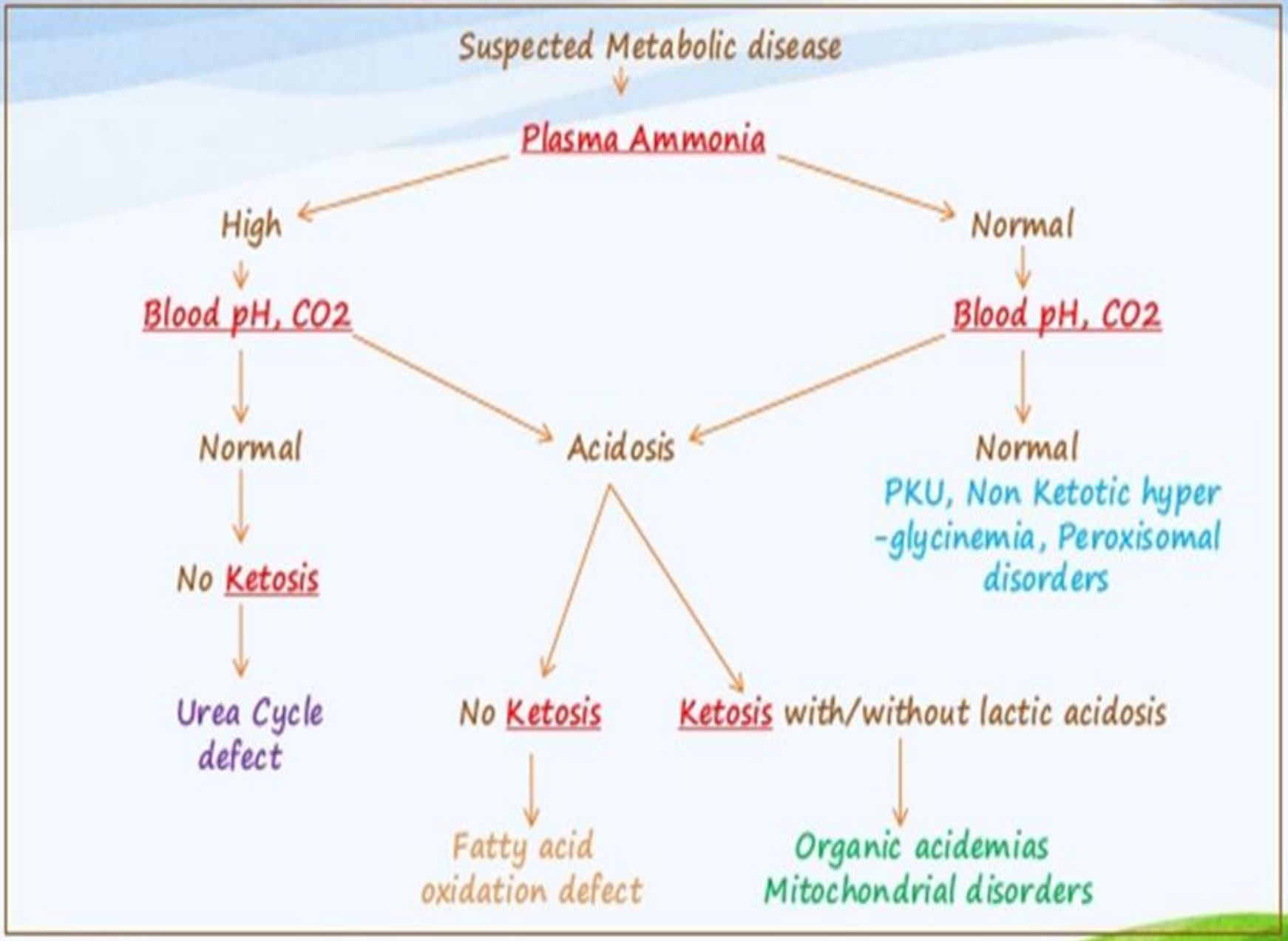


- liver function test
- blood sugar
- serum ca, mg
- Plasma amino acids assay
- Urine for -;

    1-reducing substance

    2- ketones

    3- organic acid


Suspected Metabolic disease
Plasma Ammonia
High
Normal
Blood pH, CO2
Blood pH, CO2
Normal
Acidosis
Normal
PKU, Non Ketotic hyper -glycinemia, Peroxisomal disorders
No Ketosis
Urea Cycle defect
No Ketosis
Ketosis with/without lactic acidosis
Fatty acid oxidation defect
Organic acidemias
Mitochondrial disorders

❖ Diagnosis is important

- for treatment

(to avoid death and brain damage)

- for genetic counselling
- antenatal diagnosis in subsequent pregnancy.

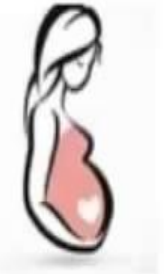
- Phenylketonurea
- Autosomal recessive
- Due to phenylalanine hydroxylase def.
- If not treated lead to mental retardation and microcephaly
- Specific odor mosey smell
- Treatment diet low in phenylalanine

*Fair hair
*Blue eyes
*Dry Skin
*Albinism

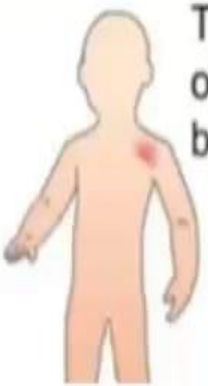
*Mental Retardation

*Athetosis
*Seizures

Pregnant women with PKU
Look for phenylalanine level
Its excess can cause Microcephaly
At the fetus.

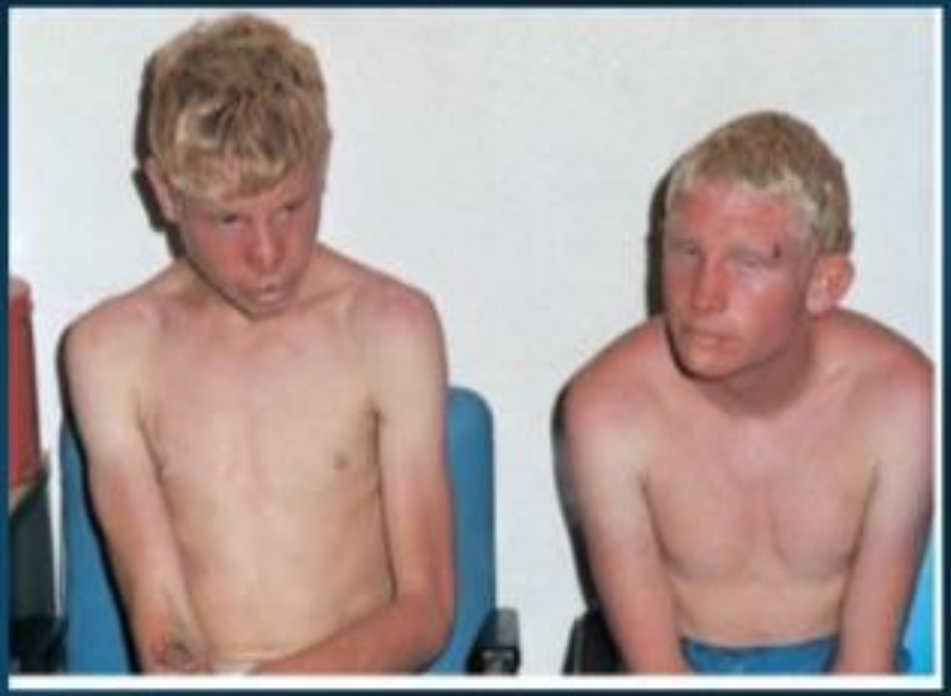


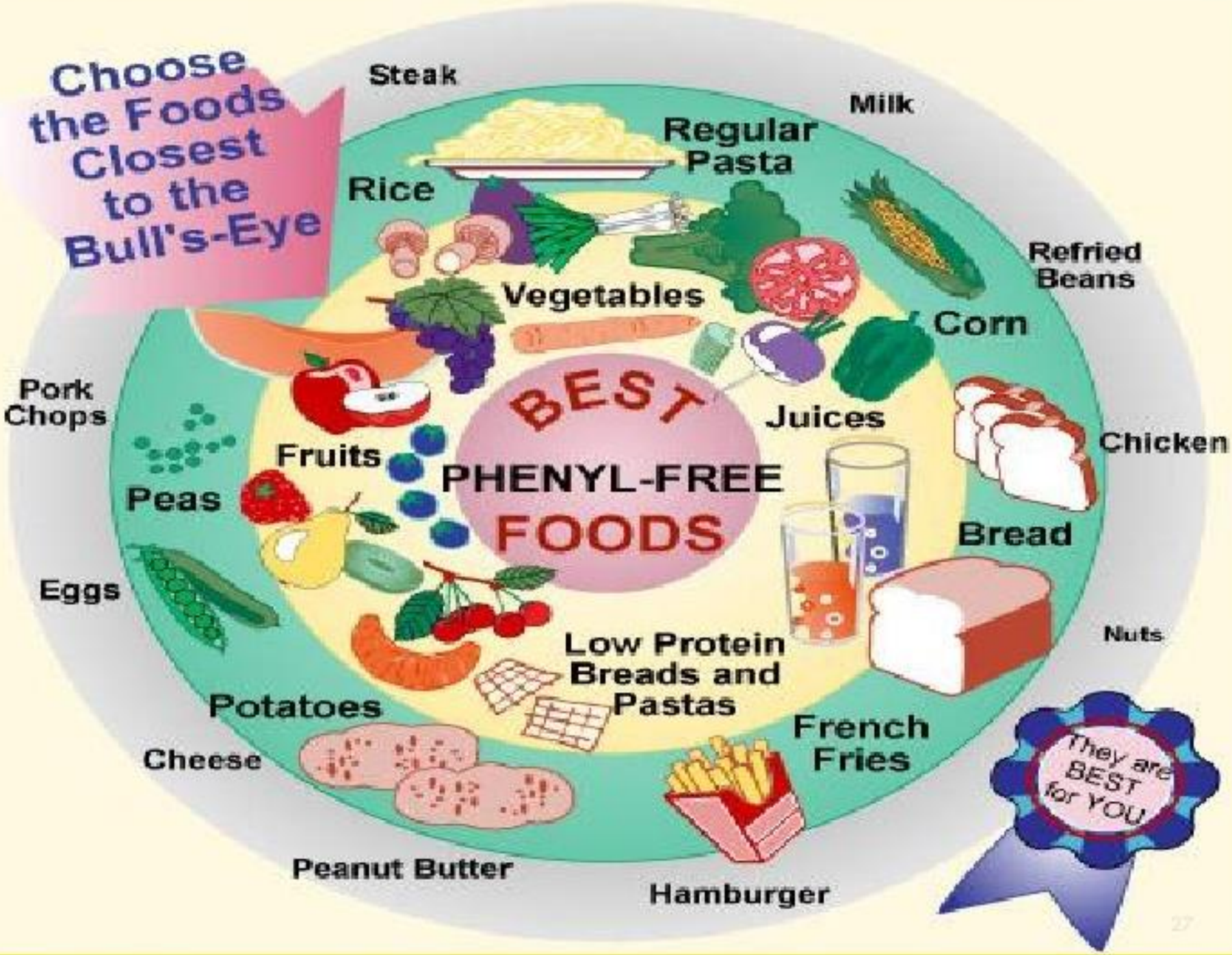
Untreated PKU sometimes makes the child smell musty. This is because the buildup of phenylalanine is in their breath, urine and sweat.



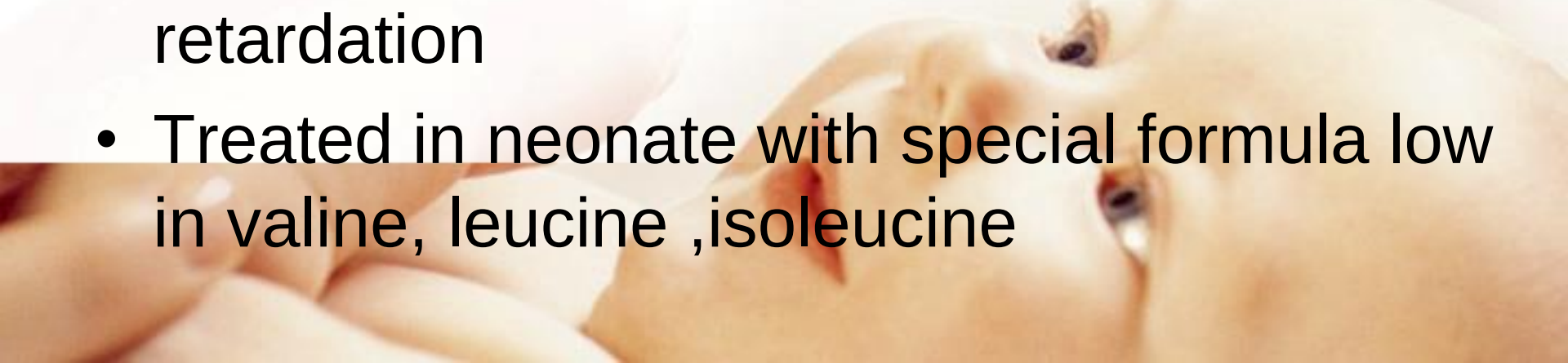
- Low Phe diet.

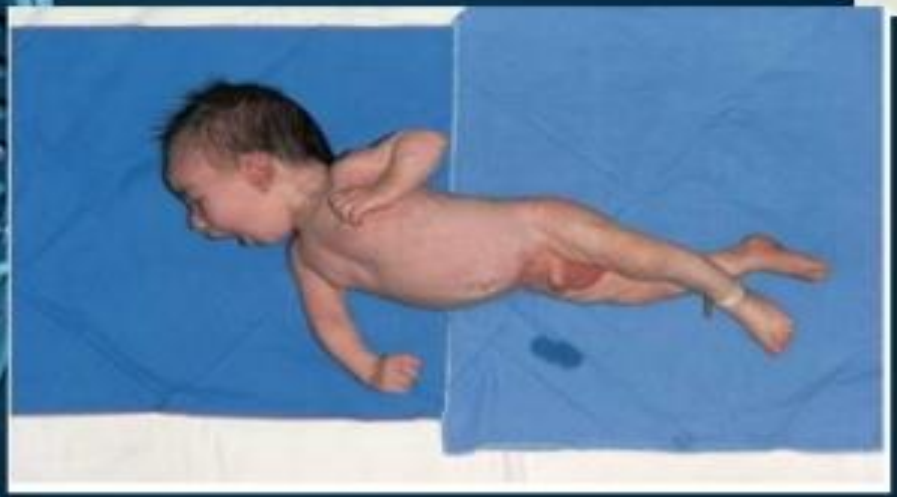
Low protein product	Fruit or vegetable	Amino acids



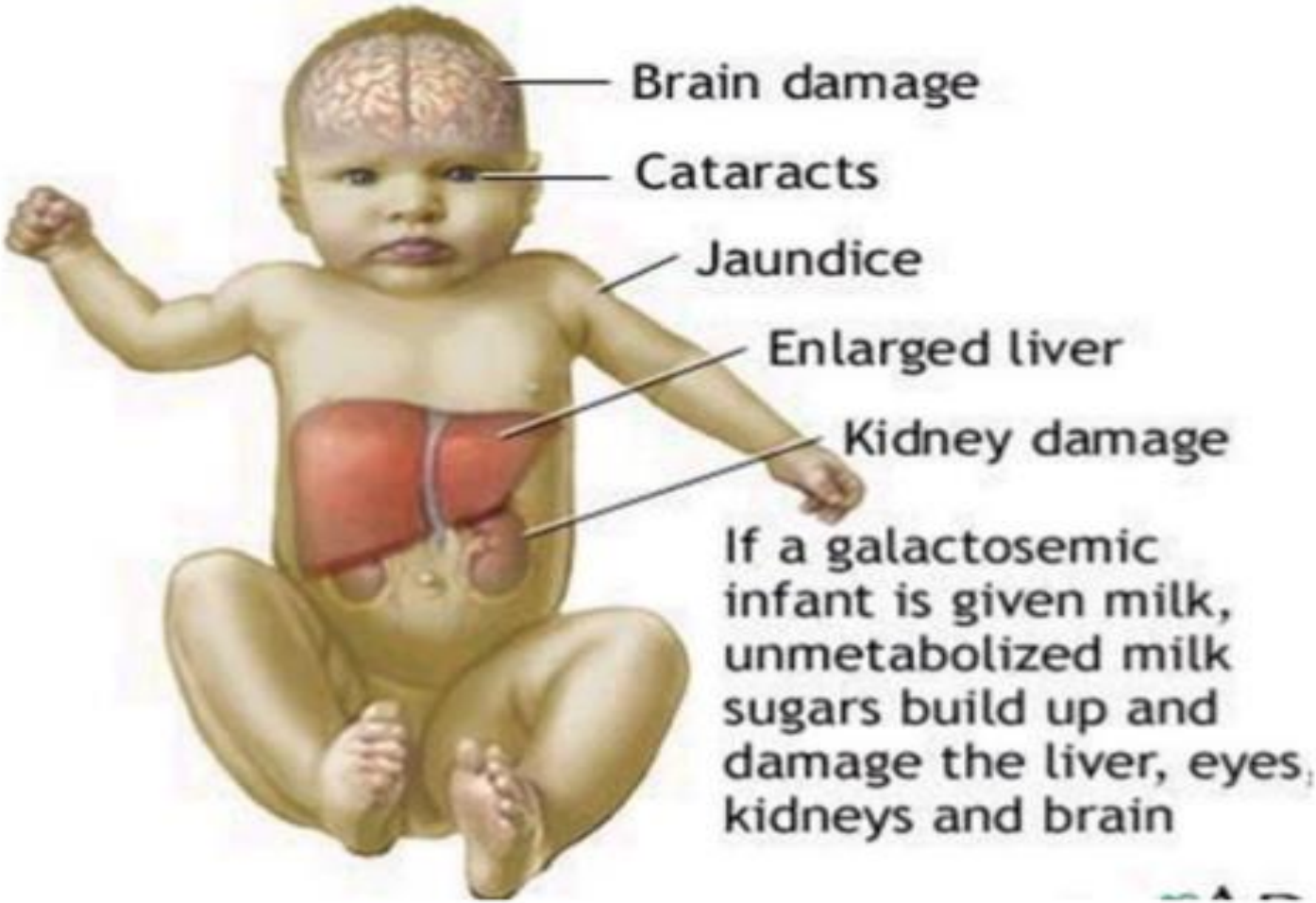

Choose the Foods Closest to the Bull's-Eye
Steak
Milk
Regular Pasta
Rice
Refried Beans
Vegetables
Corn
Pork Chops
BEST
Juices
Chicken
Fruits
PHENYL-FREE
Peas
FOODS
Bread
Eggs
Nuts
Low Protein Breads and Pastas
Potatoes
French Fries
Cheese
They are BEST for YOU
Peanut Butter
Hamburger

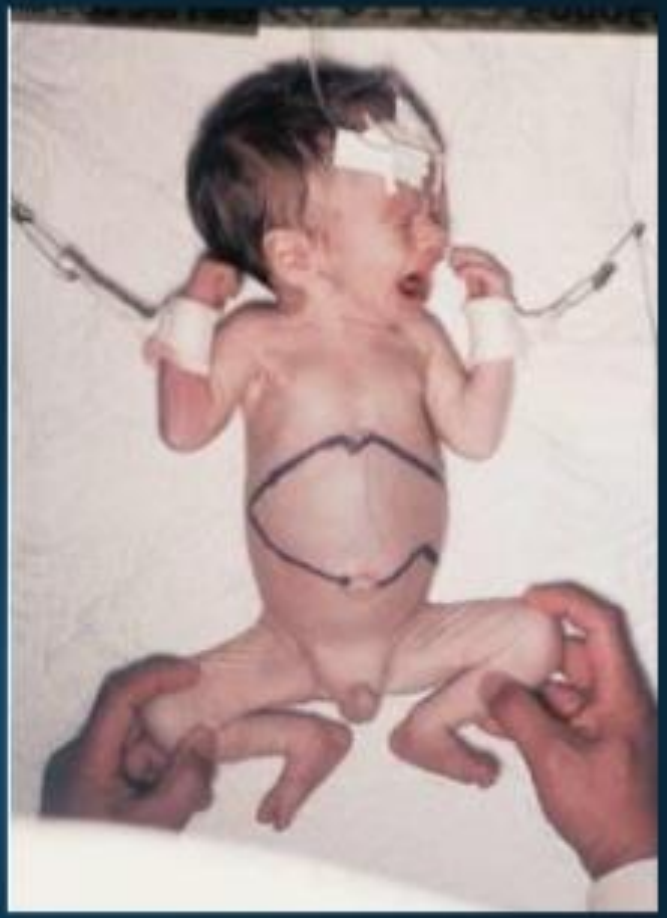
- Maple syrup urine disease
- Autosomal recessive
- branched chain 3-keto acid dehydrogenase
- Lead to high level of leucine, isoleucine and valine
- Plasma amino acid assay,urine organic acid
- Presented with acute encephalopathy;metabolic acidosis ,mental retardation
- Treated in neonate with special formula low in valine, leucine ,isoleucine



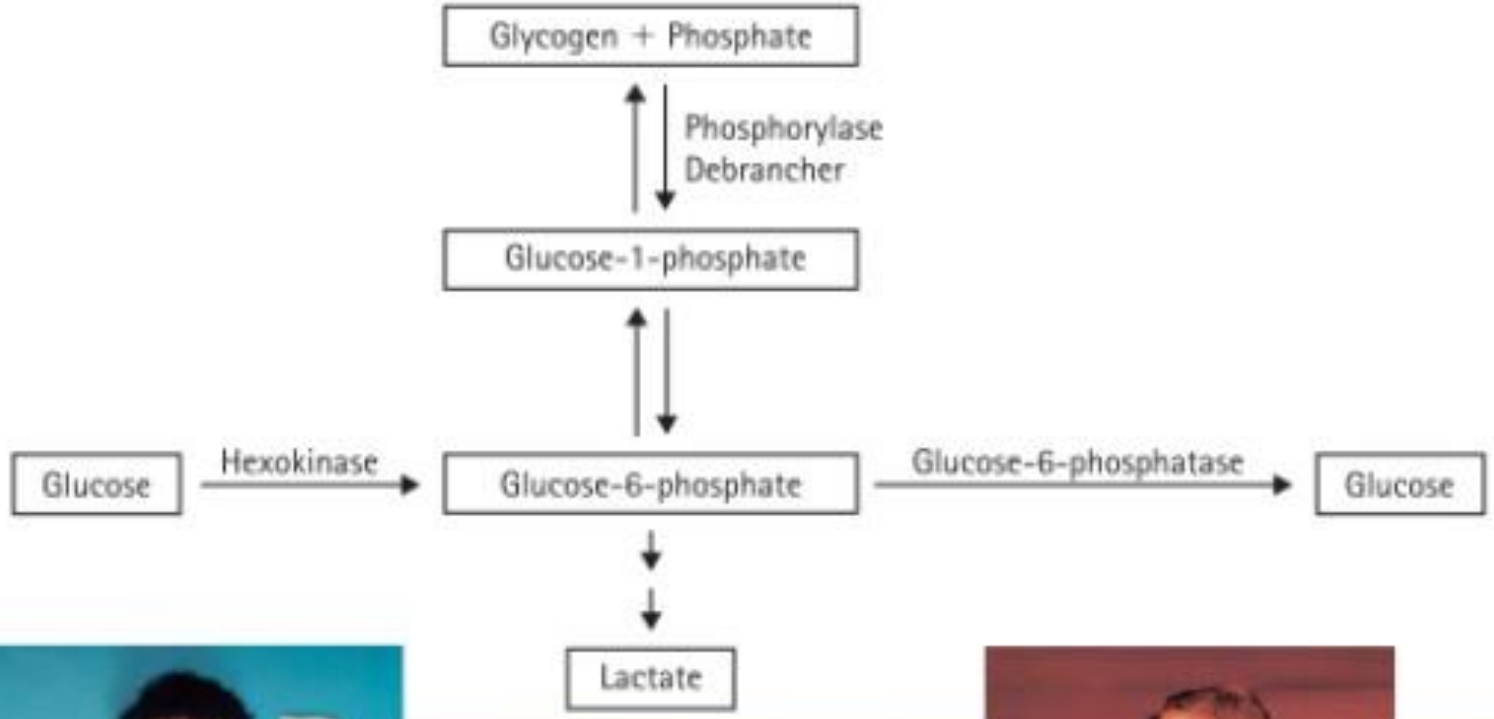


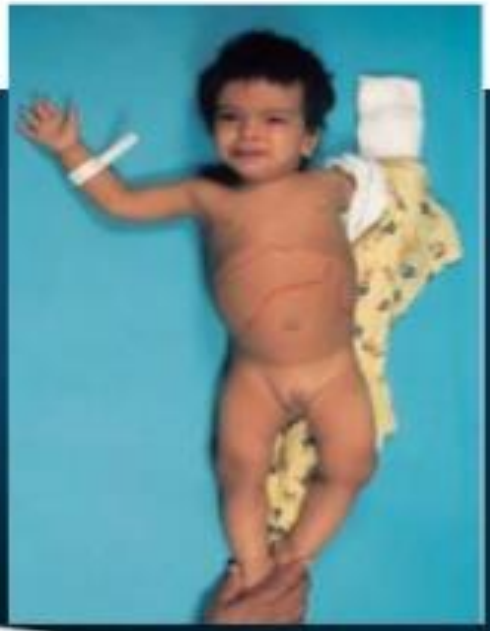
- Glactosemia
- Autosomal recessive
- Defect in galactose-1-phosphate uridyltransferase
- Presented with vomiting, jaundice, hypoglycemia, liver failure ,cataract
- Urine reducing substance +ve
- Common bacterial infection E.coli
- Treatment lactose free formula
- Prognosis good if diagnosed early

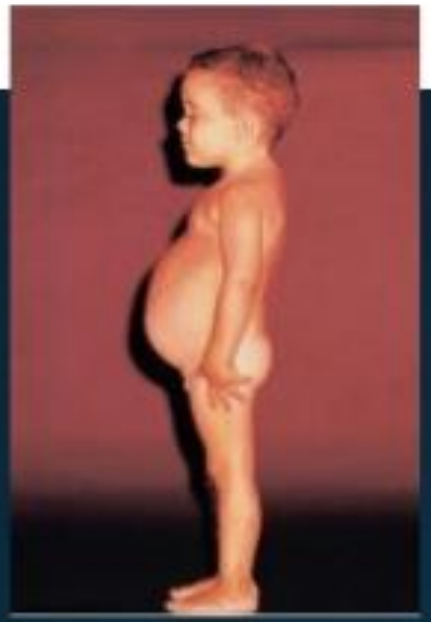

Brain damage
Cataracts
Jaundice
Enlarged liver
Kidney damage
If a galactosemic infant is given milk, unmetabolized milk sugars build up and damage the liver, eyes, kidneys and brain



- Glycogen storage disease type Ia
- Autosomal recessive
- Defect in glucose -6-phosphate
- Presented with intractable hypoglycemia not respond to glucagon , lactic acidosis later with liver dysfunction ,hyperlipidemia
- Diagnosis by liver biopsy ,enzyme assay
- Treat with corn starch ,over night feeding


Glycogen + Phosphate
Phosphorylase
Debrancher
Glucose-1-phosphate
Glucose
Hexokinase
Glucose-6-phosphate
Glucose-6-phosphatase
Glucose
Lactate





- Glycogen storage disease type II

  pompe’s disease ---- autosomal recessive

lysosomal acid alpha-glycosidase deficiency

can built up glycogen lead to muscle weakness

--facial muscle weakness—difficult in feeding-

---restrictive cardiomyopathy ,hepatomegaly

---need physiotherapy to strengthen the muscle

Diet high in protein

Enzyme supplement

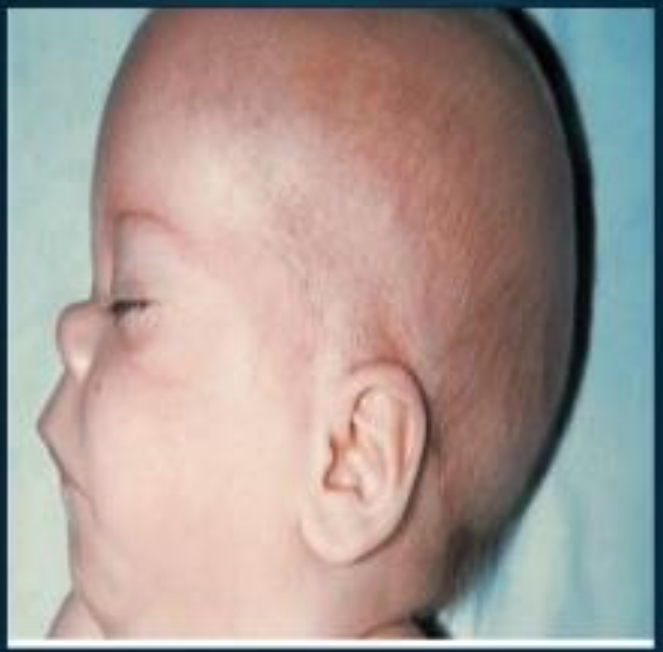
SIGNS OF POMPE DISEASE
in Infants

- Feeding difficulties
- Heart complications
- Breathing difficulties
- **Muscle weakness**

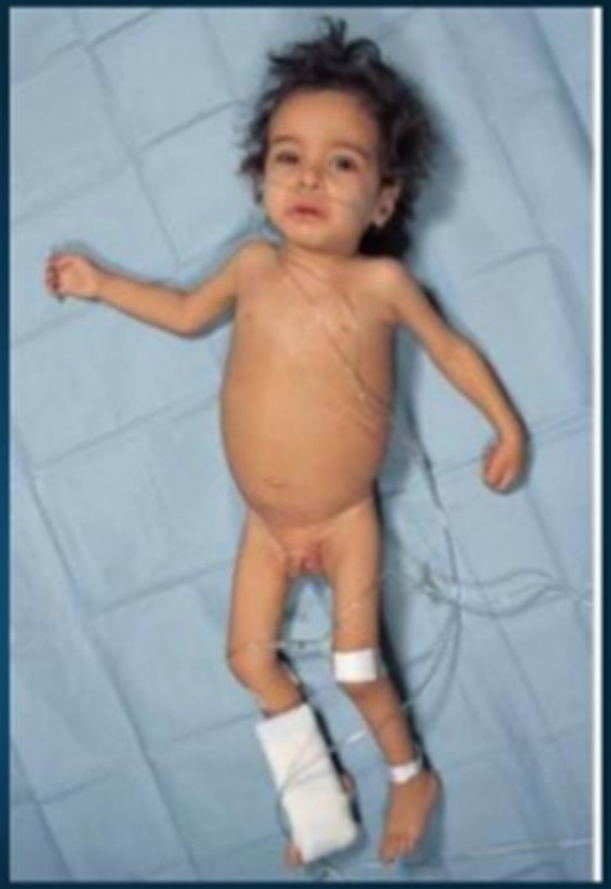
MUSCLE WEAKNESS

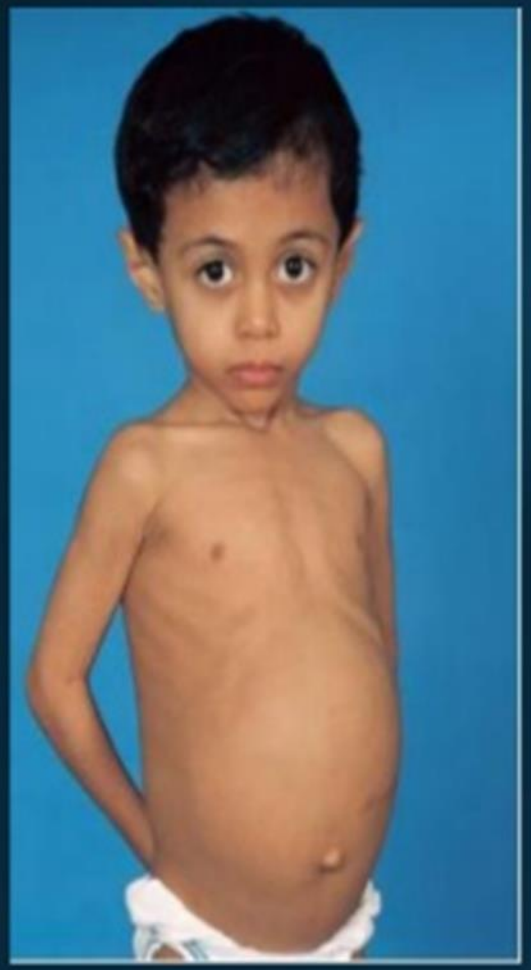
Overall muscle weakness and poor muscle tone can cause a "floppy" appearance and problems with movement.

- Lactic academia
- X-linked inheritance
- Defect in pyruvate dehydrogenase
- Present with hypoglycemia ,failure to thrive ,lactic acidosis ,seizure ,dysmorphic features
- Diagnosis plasma lactate ,enzyme assay
- Treatment
- Correct acidosis ,high fat ,low carbohydrate diet

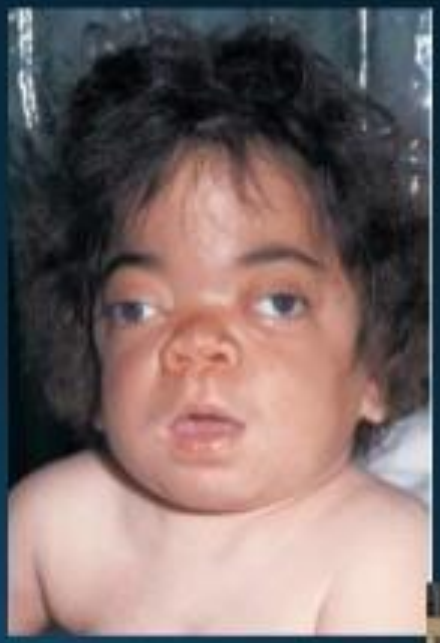


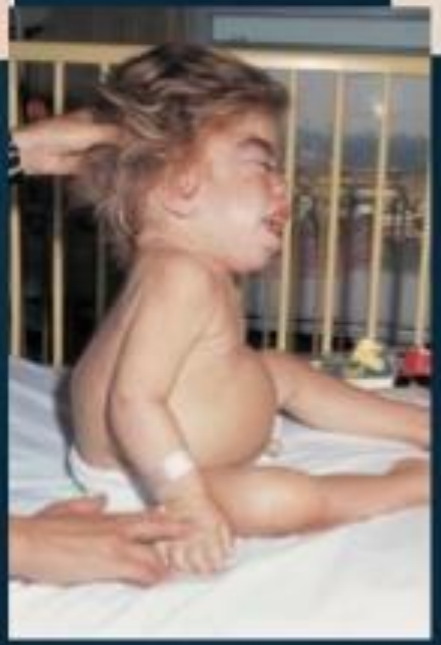
- Gaucher disease
- Autosomal recessive
- Defect in glucocerebrosidase lead to accumulation of glucocerebroside in WBC, in liver, spleen ,bone marrow,
- Presented with coarse feature ,hepatosplenomegly ,anemia thrombocytopenia due bone marrow infiltration
- Leukocyte enzyme assay .gaucer cell in bone marrow.
- Treatment enzyme replacement, bone





- Mucopolysacchridosis type I Hurler’s syndrome
- Autosomal recessive
- Defect in alpha-L-iduronidase
- Coarse feature ,hepatosplenomegaly ,corneal cloudy, skeletal dysplasia
- Diagnosis enzyme assay
- Treatment bone marrow transplant, enzyme replacement
-

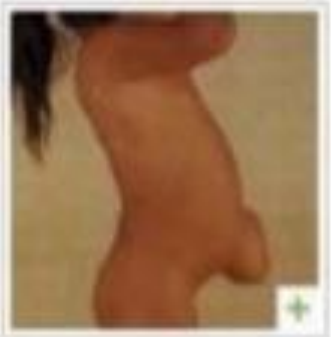




Mucopolysaccharidosis I (MPS I) Disease (Hurler, Hurler-Scheie, Scheie Syndromes)

SYMPTOMES IMAGES OF KEY FEATURES

Hernia



corneal clouding

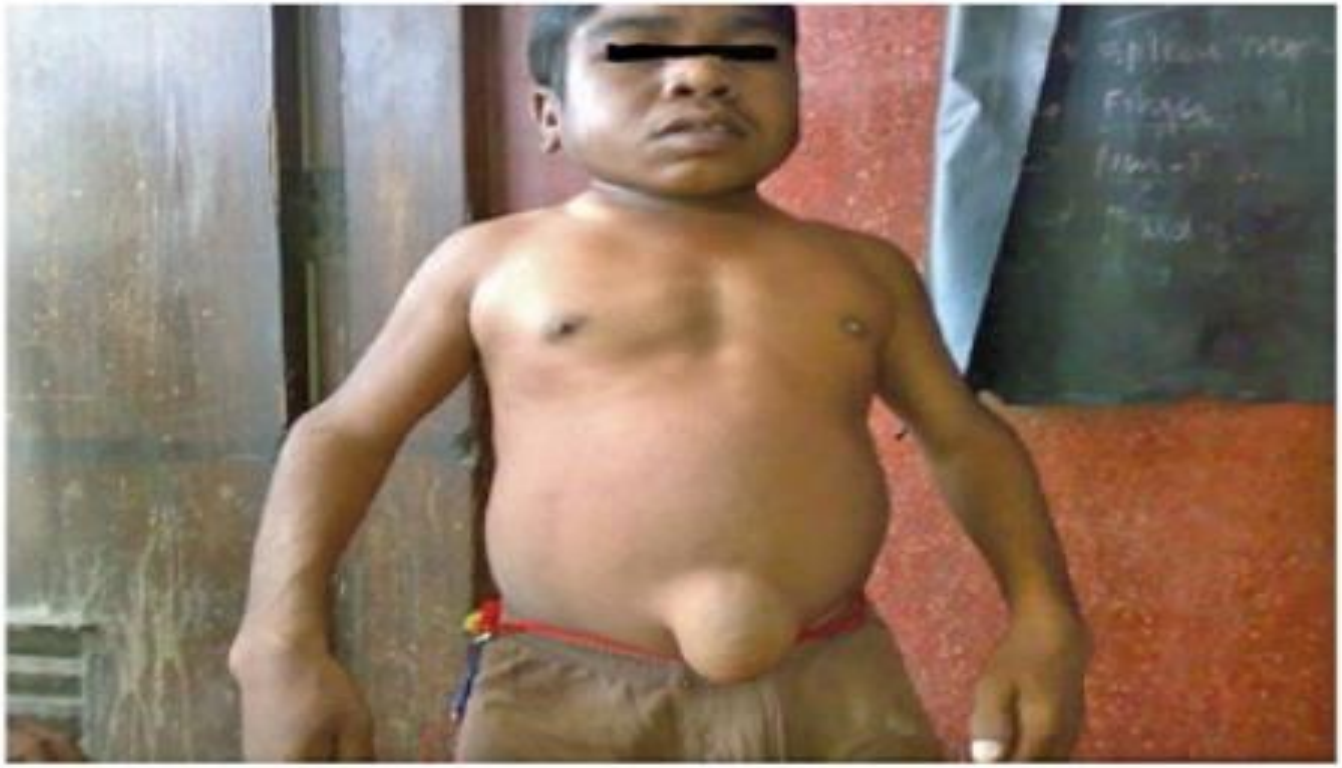
Coarse facial

Claw hand

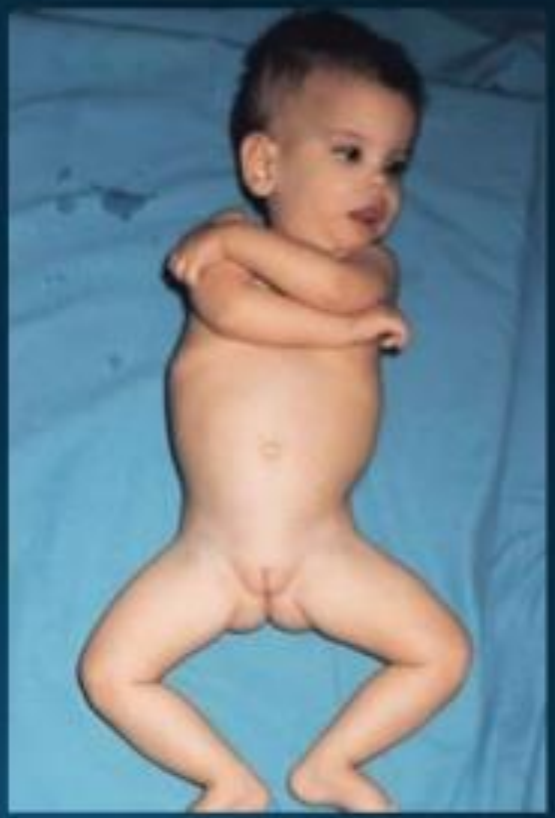
- Mucopolysaccharidase II

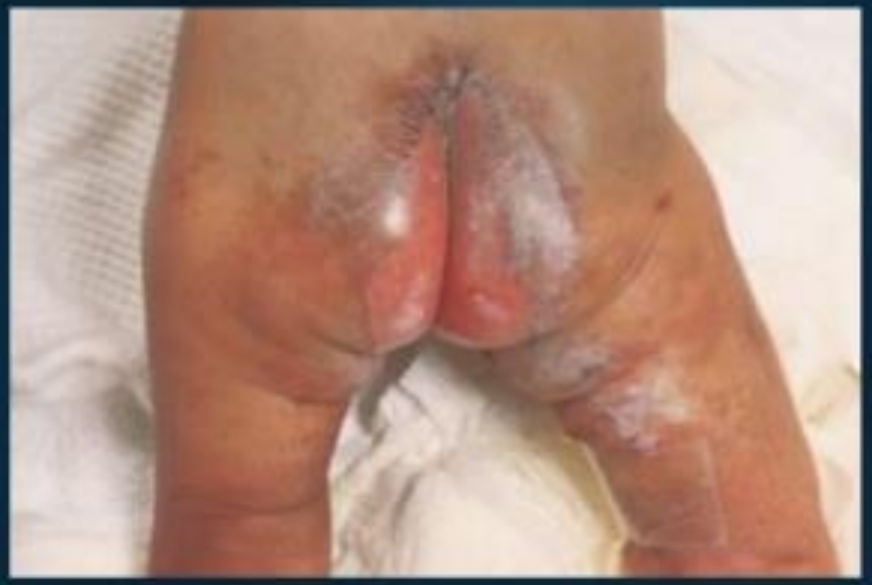
  Hunter syndrome
- X linked inheritance
- Defect in iduronate -2- sulfatase
- No corneal cloudy

Hunter syndrome with umblical hernia

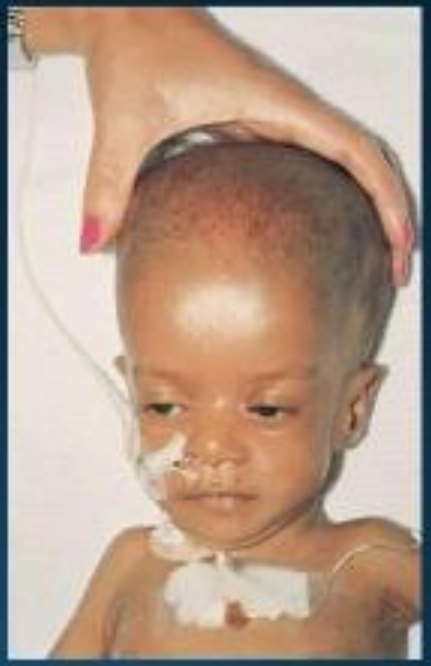
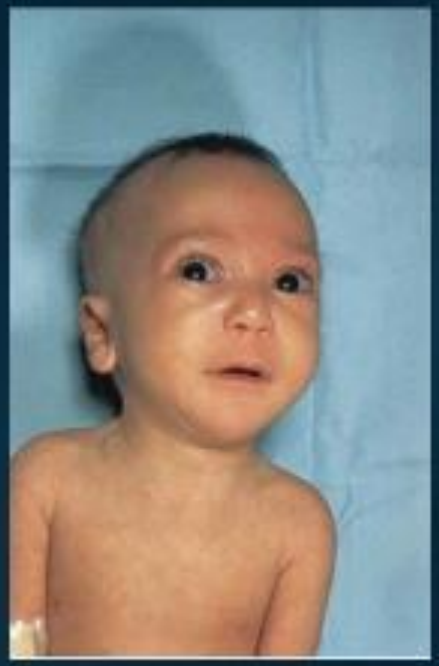


- Organic aciduria
- Methylmalonic academia
- Autosomal recessive
- Presented with acute encephalopathy with sever acidosis ,hyperammonemia ,seizer unusual oder (sweaty feet)
- Diagnosis –neutropenia, thrombocytopenia ,Metabolic acidosis, high ammonia,
- Plasma amino acid and urine organic acid
- Treatment sodium bicarbonate to treat acidosis ,carnitine ,vit 12,low protein diet





- Zellweger syndrome
- *Autosomal recessive*
- Dysmorphic feature ,sever hypotonia, seizer ,liver dysfunction ,
- Hepatomegaly ,cataract
- Plasma level of very long chain fatty acid
- No specific treatment


Large fontanelle - prominent forehead - flat nasal bridge- hypoblastic supraorbital ridges

- Urea cycle
- Ornithine transcarbamylase deficiency
- X - linked inheritance
- Presented by acute encephalopathy
- High ammonia level ,plasma amino acid and urine for orotic acid
- Treatment
- acute stage my need dialysis
- Treat hyperammonia by sodium benzoate arginine
- Low protein diet , essential amino acids

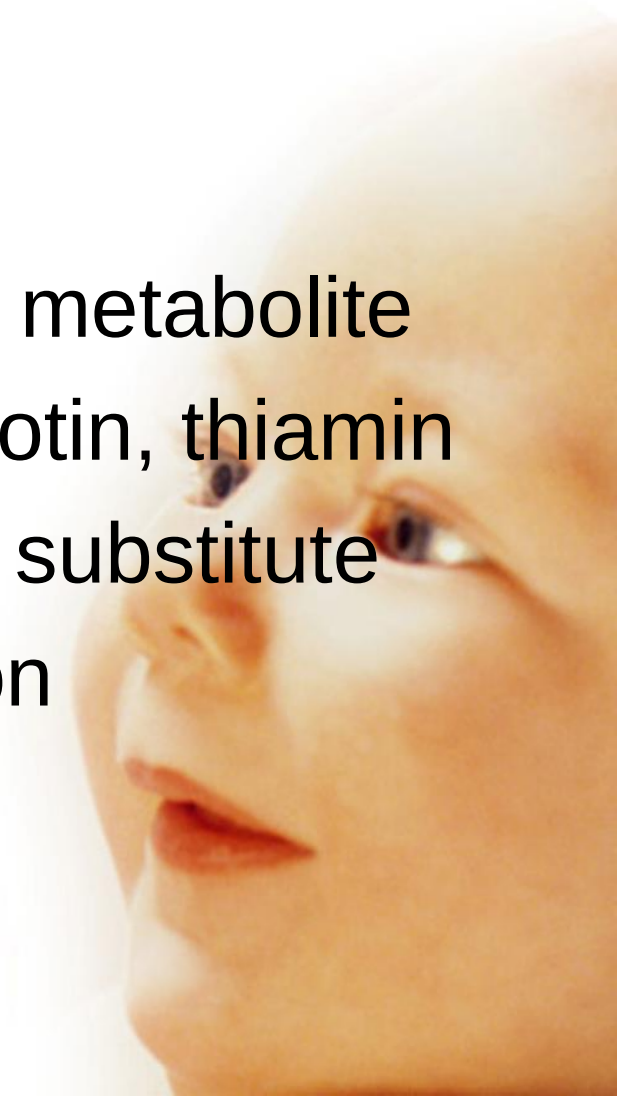
Treatment

1- reduce the formation of toxic metabolite by stopping feeding

2- provide adequate calories

3- to enhance excretion of toxic metabolite

4- to institute cofactor -- B12, biotin, thiamin pyridoxine ,folate , carnitine substitute can be in fatty acid oxidation



- 5- supportive therapy
- treatment of seizer
- Correct hypoglycemia and hypothermia
- Adequate hydration
- Correct electrolyte disturbance and acidosis
- Aggressive antibiotic therapy
- Mechanical ventilator if needed

- Management of hyperammonemia

➢ Discontinued all feeds

➢ Provide I.V. glucose and lipid

➢ Dialysis , hemodialysis faster than peritoneal dialysis ,exchange transfusion not used

➢ Drugs –sodium benzoate, sodium phenylaetate ,or sodium phenylbaturate.

➢ Ventilator support

- Long term management

A. dietary therapy

❑mainstay of phenylketonuria,

maple syrup urine disease

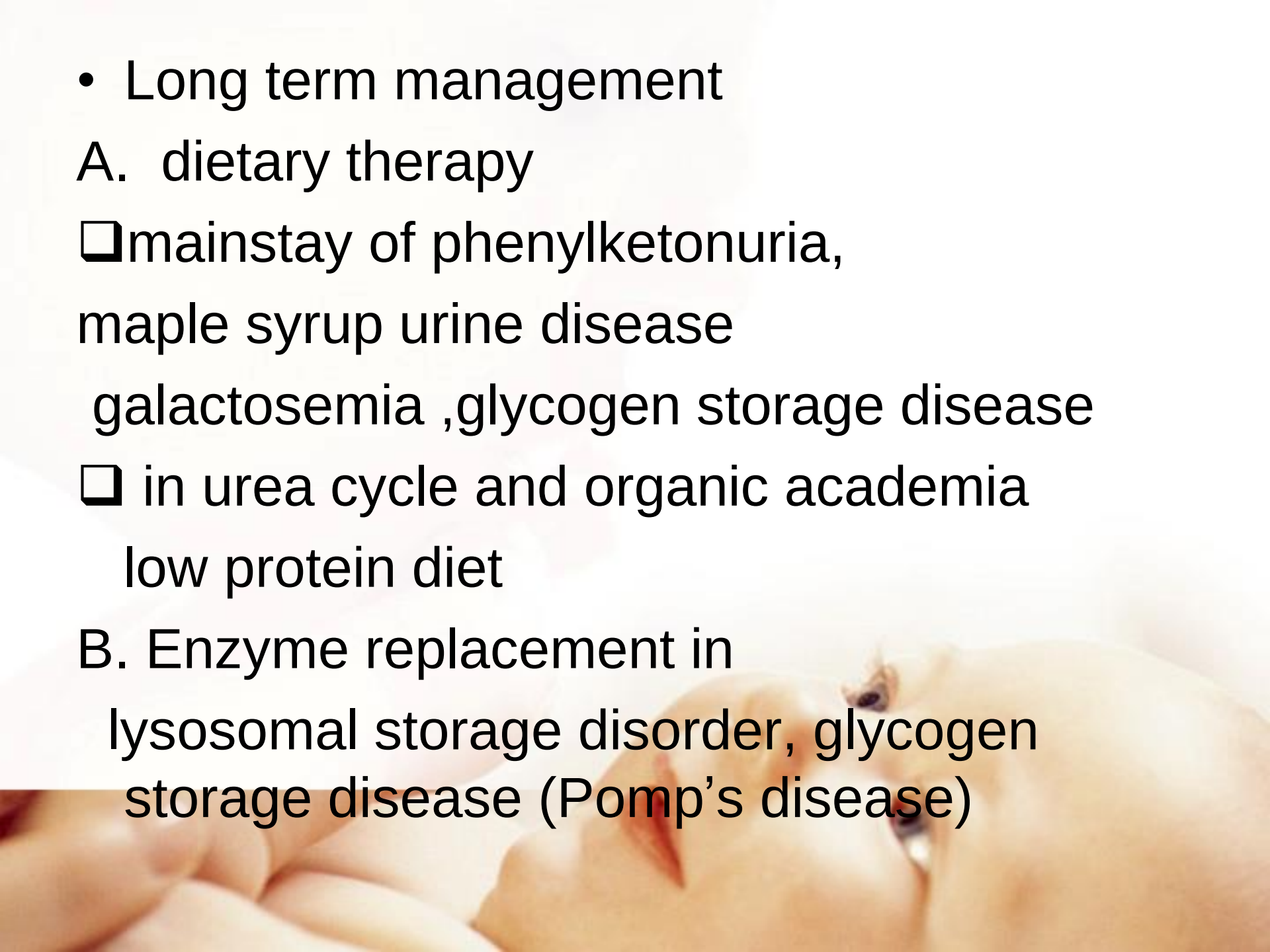
galactosemia ,glycogen storage disease

❑ in urea cycle and organic academia

low protein diet

B. Enzyme replacement in

lysosomal storage disorder, glycogen storage disease (Pomp's disease)



- Prevention

❑ prenatal diagnosis

sample

1-chorionic villous tissue(1st trimester)

2-amniotic fluid (2nd trimester)

For-; 1-metabolite detection

phenylketonuria ,peroxisomal disorder

2-enzyme assay (gaucher disease)

3-DNA based diagnosis

- Neonatal screening

Tandem mass spectrometry

diagnose a large no. of metabolic disease

highly sensitive and specificity low

some time difficult in interpretation


Thank you !!!